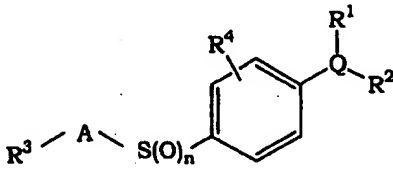




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b>  <b>C07D 231/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 00/18741</b>  <b>(43) International Publication Date:</b> 6 April 2000 (06.04.00)
<b>(21) International Application Number:</b> PCT/JP99/05289  <b>(22) International Filing Date:</b> 27 September 1999 (27.09.99)  <b>(30) Priority Data:</b> PP 6231 30 September 1998 (30.09.98) AU PQ 2243 16 August 1999 (16.08.99) AU  <b>(71) Applicant (for all designated States except US):</b> FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KONISHI, Nobukiyo [JP/JP]; 22-7, Aotanai, Nagaokakyo-shi, Kyoto 617-0811 (JP). NAKAMURA, Katsuya [JP/JP]; 12-1-103, Kamihamuro 2-chome, Takatsuki-shi, Osaka 569-1044 (JP). YAMAMOTO, Hirofumi [JP/JP]; 1-4-22-207, Kashio, Takarazuka-shi, Hyogo 665-0054 (JP). MANABE, Takashi [JP/JP]; 1-2-103, Maruyamada, Kawanishi-shi, Hyogo 666-0152 (JP).  <b>(74) Agent:</b> TAKASHIMA, Hajime; Yuki Building, 3-9, Hiranomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-0046 (JP).		<b>(81) Designated States:</b> BR, CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> NOVEL COMPOUNDS  <div style="text-align: center;">  </div> <p style="text-align: right;">(I)</p>		
<b>(57) Abstract</b>  <p>A compound of formula (I), wherein R<sup>1</sup> is halo(lower)alkyl, halogen or cyano, R<sup>2</sup> is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, lower alkoxy, cyano, nitro, lower alkenyl, amino, acyl and hydroxyimino, R<sup>3</sup> is hydrogen, hydroxy, acyloxy, lower alkoxy optionally substituted with lower alkoxy, amino optionally substituted with hydroxy or lower alkyl, lower alkylthio, or lower alkylsulfonyl, R<sup>4</sup> is hydrogen or halogen, Q is pyrazolyl, A is lower alkylene optionally substituted with oxo or hydroxy, and n is 0, 1 or 2, provided that when R<sup>3</sup> is hydrogen, R<sup>2</sup> is aryl substituted with lower alkenyl or A is lower alkylene substituted with oxo, or its salt, processes for their preparation and pharmaceutical compositions.</p>		

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## DESCRIPTION

### NOVEL COMPOUNDS

#### Technical Field

This invention relates to novel pyrazole compounds and pharmaceutically acceptable salts thereof which have pharmacological activity, to a process for their production; and to a pharmaceutical composition containing the same.

#### Background of Art

Some pyrazole derivatives having antiinflammatory and analgesic activities have been known as described, for example, in Canadian Patent 1 130 808, and EP Patent Publication Nos. 248 594, 272 704, 293 220, 418 845 and 554 829, and WO Patent Publication Nos. 95/15315, 95/15316, 95/15317, 95/15318, 96/14302 and 97/15271.

#### Disclosure of Invention

One object of this invention is to provide novel pyrazole compounds and pharmaceutically acceptable salts thereof which have an inhibiting activity of COX-II.

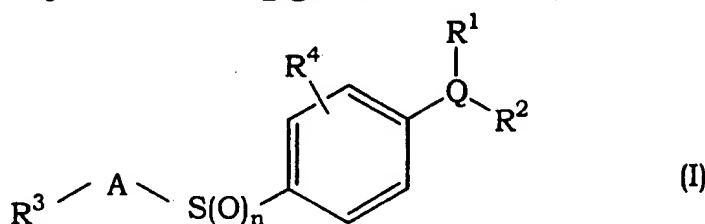
Another object of this invention is to provide a process for production of the novel pyrazole compounds.

A further object of this invention is to provide a pharmaceutical composition containing, as an active ingredient, the pyrazole compound or a pharmaceutically acceptable salt thereof.

A still further object of this invention is to provide a use of the novel pyrazole compounds and pharmaceutically acceptable salts thereof for manufacturing a medicament for treating or preventing various diseases.

The present invention relates to novel pyrazole compounds and pharmaceutically acceptable salts thereof, which have pharmaceutical activity such as inhibiting activity of cyclooxygenase-2 (hereinafter described as COX-II), to a process for their production, to a pharmaceutical composition containing the same, and to a use thereof.

The object pyrazole derivatives of this invention are new and can be represented by the following general formula (I).



wherein

$R^1$  is halo(lower)alkyl, halogen or cyano,

$R^2$  is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, lower alkoxy, cyano, nitro, lower alkenyl, amino, acyl and hydroxyimino,

$R^3$  is hydrogen, hydroxy, acyloxy, lower alkoxy optionally substituted with lower alkoxy, amino optionally substituted with hydroxy or lower alkyl, lower alkylthio, or lower alkylsulfonyl,

$R^4$  is hydrogen or halogen,

Q is pyrazolyl,

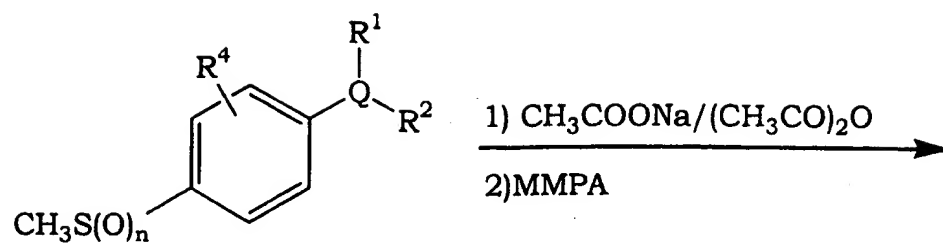
A is lower alkylene optionally substituted with oxo or hydroxy, and

n is 0, 1 or 2,

provided that when  $R^3$  is hydrogen,  $R^2$  is aryl substituted with lower alkenyl or A is lower alkyl substituted with oxo.

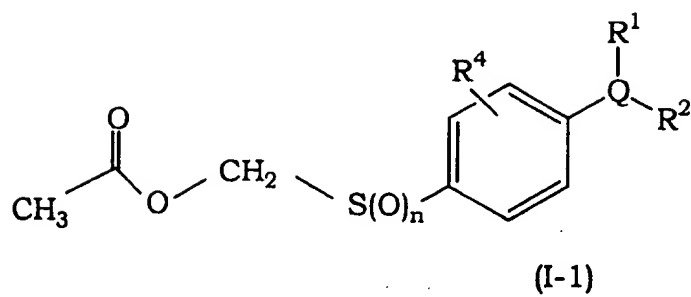
The object compound (I) can be prepared by one of the following processes 1 - 5.

#### Process 1



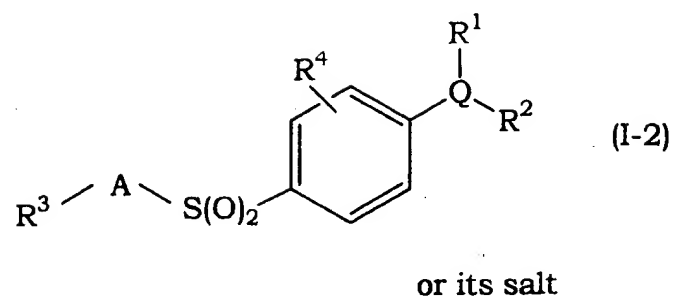
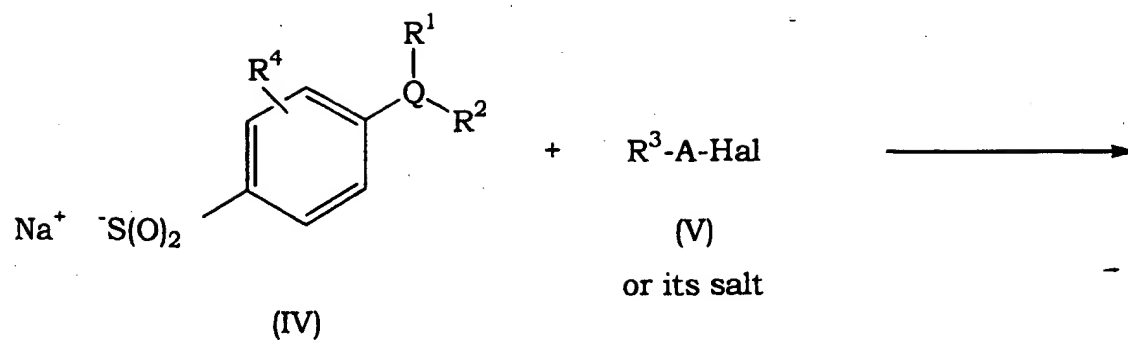
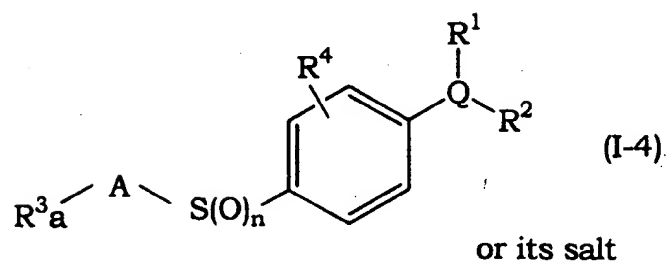
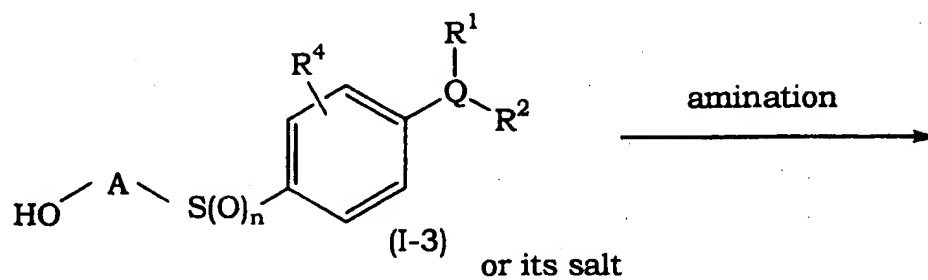
(II)

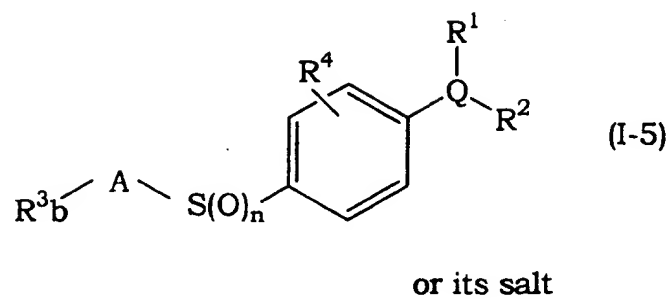
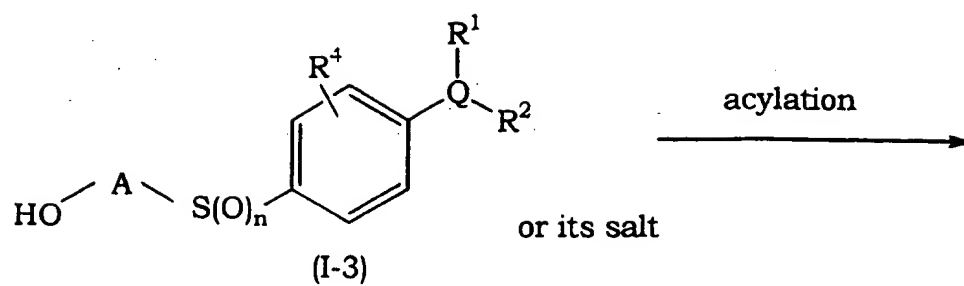
or its salt



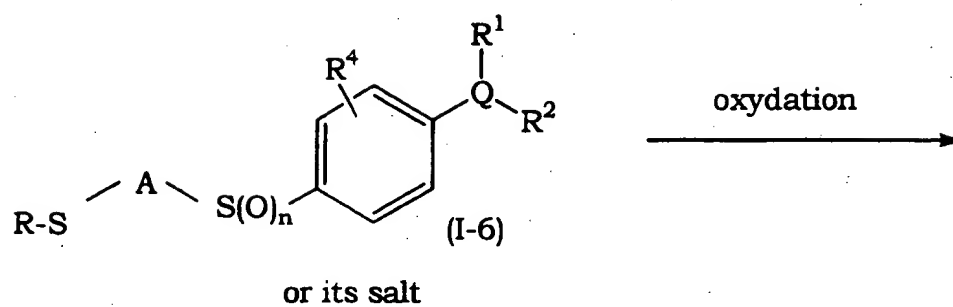
or its salt

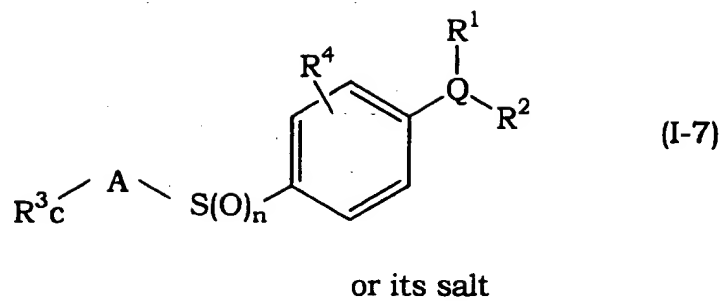
Process 2

Process 3Process 4



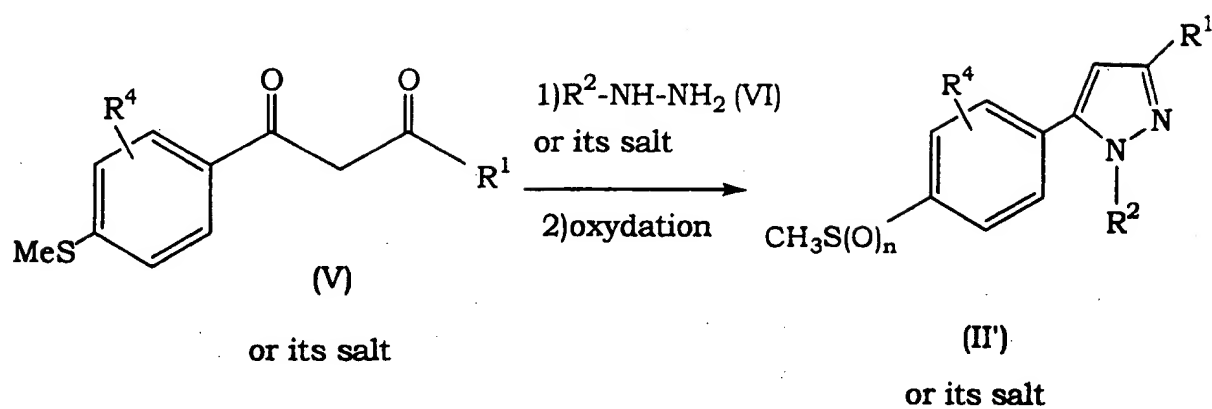
Process 5



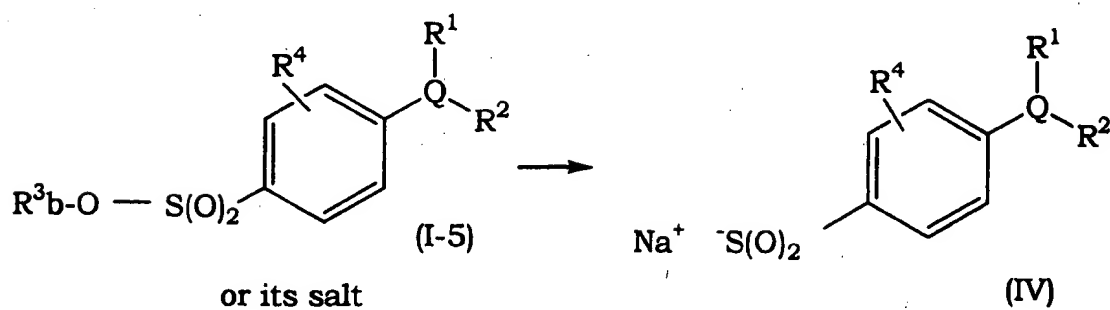


### Reference Processes

(1)



(2)



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $A$ ,  $Q$  and  $n$  are each as defined above,

$R$  is lower alkyl,



R<sup>3a</sup> is amino optionally substituted with hydroxy or lower alkyl,

R<sup>3b</sup> is acyloxy,

R<sup>3c</sup> is lower alkylsulfonyl or lower alkylsulfinyl, and

R<sup>3d</sup> is hydroxy substituted with acyl.

"Pyrazolyl" includes 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl and 5-pyrazolyl, in which preferable one is 5-pyrazolyl.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and lower alkyl moiety in the terms "lower(halo)alkyl", "lower alkylthio" and "lower alkylsulfonyl" may be a straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, hexyl, and the like, in which preferable one is C<sub>1</sub>-C<sub>4</sub> alkyl.

Suitable "lower alkenyl" includes, for example, isopropenyl, vinyl, propenyl, betenyl, pentenyl, hexenyl, in which preferable one is isopropenyl.

Suitable "lower alkoxy" includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy and hexyloxy, in which preferable one is C<sub>1</sub> - C<sub>4</sub> alkoxy.

Suitable "lower(halo)alkyl" includes, for example, trifluoromethyl, difluoromethyl, trichloromethyl, and the like.

Suitable "halogen" includes, for example, fluorine, chlorine, bromide and iodide.

Suitable "alkylene" includes, for example, methylene, dimethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, propylene, ethylidene, and the like.

Suitable "acyl" and acyl moiety in the term "acyloxy" include acyl

such as aliphatic acyl, aromatic acyl and heterocyclic acyl.

The aliphatic acyl includes saturated or unsaturated, acyclic or cyclic ones, for example, alkanoyl such as lower alkanoyl (e.g., formyl, acetyl, propionyl, butyl, isobutyl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), alkylsulfonyl, such as lower alkylsulfonyl (e.g., mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.), carbamoyl, N-alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), alkoxycarbonyl such as lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), alkenyloxycarbonyl such as lower alkenyloxycarbonyl (e.g., vinylloxycarbonyl, allyloxycarbonyl, etc.), alkenoyl such as lower alkenoyl (e.g., acryloyl, methacryloyl, crotonoyl, etc.), cycloalkanecarbonyl such as cyclo(lower)alkanecarbonyl (e.g., cyclopropanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.), and the like.

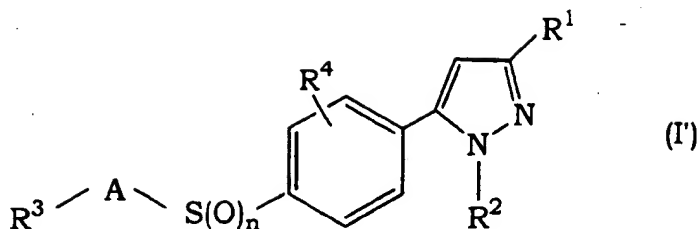
The aromatic acyl may include  $C_6 - C_{10}$  aroyl (e.g., benzoyl, toluoyl, xyloyl, etc.), N-( $C_6 - C_{10}$ )arylcarbamoyl (e.g., N-phenylcarbamoyl, N-tolylcarbamoyl, N-naphthylcarbamoyl, etc.),  $C_6 - C_{10}$  arenesulfonyl (e.g., benzenesulfonyl, tosyl, etc.), and the like.

The heterocyclic acyl may include heterocyclic carbonyl (e.g., furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, etc.), and the like.

Suitable "aryl" includes, for example, an aryl having 6 to 10 carbon atoms, such as phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, in which preferable one is phenyl and tolyl.

Each of  $R^1$  and  $R^2$  may be attached to any position of the pyrazole ring.

The preferred ones of the compound (I) are compounds having the formula (I')



wherein

$R^1$  is halo(lower)alkyl, halogen or cyano,

$R^2$  is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, lower alkoxy, cyano, nitro, lower alkenyl, amino, acyl and hydroxyimino,

$R^3$  is hydroxy, acyloxy, lower alkoxy optionally substituted with lower alkoxy, amino optionally substituted with hydroxy or lower alkyl, lower alkylthio, or lower alkylsulfonyl,

$R^4$  is hydrogen or halogen,

A is lower alkylene optionally substituted with oxo or hydroxy, and  
n is 0, 1 or 2,

provided that when  $R^3$  is hydrogen,  $R^2$  is aryl substituted with lower alkenyl or A is lower alkylene substituted with oxo, or its salt.

The most preferred ones of the compound (I) are compounds having the formula (I') wherein

$R^1$  is trifluoromethyl, difluoromethyl, chlorine or cyano,

$R^2$  is phenyl, tolyl, or phenyl or tolyl substituted with substituent(s) selected from the group consisting of chlorine, fluorine, bromine and methoxy,

$R^3$  is hydroxy, acetoxy, ethoxy, amino, methylamino, methylthio or methylsulfonyl,

$R^4$  is hydrogen,

A is dimethylene, trimethylene, methylene or pentamethylene, and  
n is 2.

The preferred one is the compound selected from the group consisting of

- (1) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-chloro-4-methoxyphenyl)pyrazole,
- (2) 5-[4-(acetoxymethylsulfonyl)phenyl]-1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole,
- (3) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (4) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (5) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (6) 1-(3-chloro-4-methoxyphenyl)-5-{4-[[2-(methylthio)ethyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (7) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(5-hydroxypentyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (8) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(4-hydroxybutyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (9) 1-(3-chloro-4-methoxyphenyl)-5-[4-(ethoxycarbonylmethylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole,
- (10) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-methylaminoethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (11) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-aminoethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (12) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-acetoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (13) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-acetoxyethyl)sulfonyl]phenyl}pyrazole,
- (14) 1-(3-chloro-4-methoxyphenyl)-5-{4-[[2-(methylsulfonyl)ethyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (15) 5-{4-[(acetoxymethyl)sulfonyl]phenyl}-1-(4-fluorophenyl)-3-(trifluoromethyl)pyrazole,
- (16) 1-(4-fluorophenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-

- (trifluoromethyl)pyrazole,
- (17) 5-{4-[(acetoxymethyl)sulfonyl]phenyl}-1-(4-chloro-3-methoxyphenyl)-3-cyanopyrazole,
- (18) 1-(4-chloro-3-methoxyphenyl)-5-{4-[2-hydroxyethyl)sulfonyl]phenyl}-3-cyanopyrazole,
- (19) 5-[4-(acetoxymethylthio)phenyl]-1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazole,
- (20) 5-[4-(acetoxymethylsulfonyl)phenyl]-1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazole,
- (21) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-methylphenyl)-pyrazole,
- (22) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-methylphenyl)-pyrazole,
- (23) 3-chloro-1-(4-isopropenylphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole,
- (24) 5-[(4-acetoxymethylthio)phenyl]-3-chloro-1-(isopropenylphenyl)-pyrazole,
- (25) 3-chloro-1-(4-isopropenylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}pyrazole,
- (26) 3-chloro-1-(4-isopropenylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (27) 1-(4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (28) 1-(4-methylphenyl)-5-{4-[(3-acetoxypentyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (29) 1-(4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (30) 5-[4-(acetoxymethylthio)phenyl]-3-trifluoromethyl-1-[(3-chloro-4-methyl)phenyl]pyrazole,
- (31) 1-(3-chloro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

- (32) 1-(3-chloro-4-methylphenyl)-5-{4-[(2-acetoxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (33) 1-(4-fluoro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (34) 1-(4-fluoro-3-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (35) 1-(3-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (36) 1-(3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (37) 1-(3-fluoro-4-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (38) 1-(3-fluoro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (39) 5-{4-[(acetoxymethyl)sulfinyl]-3-fluorophenyl}-1-(3-chloro-4-methoxy-phenyl)-3-(trifluoromethyl)pyrazole,
- (40) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-3-fluorophenyl}-3-(trifluoromethyl)pyrazole,
- (41) 1-(4-chloro-3-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (42) 1-(1-hydroxy-1-methylethyl)-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole,
- (43) 1-(4-isopropenylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (44) 1-(3-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (45) 1-(3-chlorophenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (46) 1-(4-isopropylphenyl)-5-[4-(acetoxymethylthio)phenyl]-3-(trifluoromethyl)pyrazole,
- (47) 1-(4-isopropylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-

- (trifluoromethyl)pyrazole,
- (48) 5-[4-(acetoxymethylsulfonyl)phenyl]-1-(3-cyano-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole,
- (49) 1-(3-cyano-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (50) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-methoxypropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (51) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(N-hydroxycarbamoyl)methylsulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (52) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(methylcarbamoyl)methylsulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (53) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-oxopropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (54) 5-{4-[(3-acetoxypentyl)sulfonyl]phenyl}-1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole,
- (55) 1-(3-chloro-4-methoxyphenyl)-5-{4-[[3-(dimethylamino)propyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole hydrochloride,
- (56) 1-(3-chloro-4-methoxyphenyl)-5-{4-[[2-(dimethylamino)ethyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole hydrochloride,
- (57) 5-[4-(acetoxymethylthio)phenyl]-1-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)pyrazole,
- (58) 1-(3-chloro-4-methoxyphenyl)-3-difluoromethyl-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (59) 1-(3-chloro-4-methoxyphenyl)-5-{4-[[2-(2-hydroxyethoxy)ethyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (60) 5-[4-(acetoxymethylthio)phenyl]-1-(4-bromo-3-methoxyphenyl)-3-(trifluoromethyl)pyrazole,
- (61) 1-(4-bromo-3-methoxyphenyl)-3-trifluoromethyl-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (62) 1-(4-bromo-3-methoxyphenyl)-3-trifluoromethyl-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

- (63) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-difluoromethyl-1-[4-(methoxyphenyl)pyrazole,
- (64) 1-(4-methoxyphenyl)-3-difluoromethyl-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (65) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-bromophenyl)-pyrazole,
- (66) 1-(3-bromophenyl)-3-chloro-5-{4-(3-hydroxypropyl)sulfonyl}phenyl}pyrazole,
- (67) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-fluoro-4-methylphenyl)pyrazole,
- (68) 3-chloro-1-(3-fluoro-4-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (69) 5-[[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-fluoro-3-methylphenyl)pyrazole,
- (70) 3-chloro-1-(4-fluoro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (71) 3-chloro-1-(4-fluoro-3-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (72) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (73) 1-(3-chlorophenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (74) 3-chloro-1-(4-isopropenylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (75) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}pyrazole hydrochloride,
- (76) 5-[4-(4-acetoxymethylthio)phenyl]-3-chloro-1-(4-chloro-3-methylphenyl)pyrazole,
- (77) 3-chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (78) 3-chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(3-hydroxypropyl)-



- sulfonyl]phenyl}pyrazole,
- (79) 3-chloro-1-(3-chloro-4-methylphenyl)-5-{4-[(3-hydroxypropyl)-sulfonyl]phenyl}pyrazole,
- (80) 3-chloro-1-(3-chloro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)-sulfonyl]phenyl}pyrazole,
- (81) 3-chloro-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-1-(4-methylphenyl)pyrazole,
- (82) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(3-methylphenyl)pyrazole,
- (83) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-methylphenyl)-pyrazole,
- (84) 3-chloro-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-1-(3-methylphenyl)pyrazole,
- (85) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-phenylpyrazole,
- (86) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-phenylpyrazole,
- (87) 3-chloro-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-1-phenylpyrazole,
- (88) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-chloro-3-methoxyphenyl)pyrazole,
- (89) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-chloro-3-methoxyphenyl)pyrazole,
- (90) 3-chloro-1-(4-chloro-3-methoxyphenyl)-5-{4-[(3-hydroxypropyl)-sulfonyl]phenyl}pyrazole,
- (91) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(3-chlorophenyl)-pyrazole,
- (92) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-chlorophenyl)-pyrazole,
- (93) 3-chloro-1-(3-chlorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (94) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-chlorophenyl)-pyrazole,

- (95) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-chlorophenyl)-pyrazole,  
(96) 3-chloro-1-(4-chlorophenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-pyrazole,  
(97) 3-chloro-1-(4-chlorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,  
(98) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-fluorophenyl)-pyrazole,  
(99) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-fluorophenyl)-pyrazole,  
(100) 3-chloro-1-(4-fluorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,  
(101) 5-(4-methylphenyl)-1-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,  
(102) 5-(4-methylphenyl)-1-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole, and  
(103) 5-(4-chloro-3-methoxyphenyl)-1-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole.

The more preferred one is the compound selected from the group consisting of

- (1) 1-(3-chloro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,  
(2) 1-(3-fluoro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,  
(3) 1-(4-fluoro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,  
(4) 1-(4-bromo-3-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,  
(5) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,  
(6) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole.

phenyl}-3-(trifluoromethyl)pyrazole,

(7) 3-chloro-1-(4-isopropenylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}pyrazole,

(8) 3-chloro-1-(4-chlorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]-phenyl}pyrazole,

(9) 3-chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,

(10) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

(11) 3-chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole, and

(12) 5-(4-chloro-3-methoxyphenyl)-1-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole.

The compounds (I) according to the present invention may contain one or more asymmetric centers, and thus they can exist as enantiomers or diastereoisomers, and the invention includes both mixtures and separate individual isomers.

Suitable salts of the compounds (I) are conventional pharmaceutically acceptable salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt etc.), an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate,

trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like, and the preferable example thereof is an acid addition salt.

The compound (I) according to the present invention can be in the form of a solvate, which was included within the scope of the present invention. The solvate preferably includes a hydrate, an ethanolate, and so on.

Also included in the scope of invention are radiolabelled derivatives of compounds (I) which are suitable for biological studies.

#### Process 1

The compound (I-1) can be prepared by reacting the compound (II) or its salt with  $\text{CH}_3\text{COONa}$  (sodium acetate) or  $(\text{CH}_3\text{CO})_2\text{O}$  (acetic anhydride), and then the oxydation.

#### (First step)

The reaction is usually carried out at reflux temperature. The solvents to be used are conventional solvents such as water, alcohol [e.g., methanol, ethanol, isopropanol, etc.], alkanolic acid, tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof, preferably, acidic solvent such as alkanolic acid (e.g., acetic acid).

#### (Oxydation)

The oxidizing agent to be used is MMPAC (magnesium monoperoxyphthalate).

This reaction is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [e.g. methanol, ethanol, etc.], a mixture thereof or the like.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

### Process 2

The compound (I-2) can be prepared by reacting a compound (IV) or its salt with a compound (V) or its salt.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropanol, etc.], alkanolic acid, tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof, preferably, acidic solvent such as alkanolic acid (e.g., acetic acid).

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

### Process 3

The compound (I-4) or its salt can be prepared from the compound (I-3) or its salt.

Amination can preferably be carried out by, for example, reacting the compound (I-4) with a mesylating reagent such as methanesulfonyl chloride and methanesulfonic anhydride to give a mesylate. The solvents to be used are, for example, dichloromethane, chloroform, tetrahydrofuran, or any other organic solvents which do not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Then, the mesylate is reacted with an alkylamine (e.g., methylamine, dimethylamine, ethylamine, etc.) or hydroxyamine. The solvents to be used are, for example, acetonitrile, tetrahydrofuran, toluene, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

### Process 4

The compound (I-5) can be prepared from the compound (I-3).

The acylating agent to be used are, for example, a lower alkanolic anhydride (e.g., acetic anhydride, etc.), lower alkanoyl halide (e.g., acetyl chloride, etc.), and the like.

The reaction is usually carried out in a solvent such as dichloromethane, tetrahydrofuran, toluene, a solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out under cooling to warming.

#### Process 5

The compound (I-7) can be prepared by reacting the compound (I-6) with an oxidizing agent.

The suitable oxidizing agent may be hydrogen peroxide, cumene hydroperoxide, tert-butyl hydroperoxide, Jones reagent, peracid [e.g. peracetic acid, perbenzoic acid, m-chloroperbenzoic acid, monopersulfate compound (Oxone®), etc.], chromic acid, potassium permanganate, alkali metal periodate [e.g. sodium periodate, etc.], and the like.

This reaction is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [e.g. methanol, ethanol, etc.], a mixture thereof or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

#### Reference Processes

(1) The compound (II') can be prepared by reacting the compound (V) or its salt with a hydrazine derivative (VI) or its salt.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], alkanolic acid, tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof,

preferably, acidic solvent such as alkanoic acid (e.g., acetic acid.)

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(2) The compound (IV) can be prepared from the compound (I-5) or its salt in a similar manner to that of Process 2 and below mentioned Preparations.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

Suitable salts of the compounds (II) and (V) are, for example, an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.), and the like.

The object compound (I) possesses inhibiting activity of COX-II and possesses strong antiinflammatory, analgesic, antithrombotic, anti-cancer activities and so on. The object compound (I) and pharmaceutically acceptable salts thereof, therefore, are useful for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals, and more particularly for the treatment and/or prevention of inflammation and pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel

syndrome, etc.], gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, particularly those in which lipooxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodosa, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimer's disease, and the like. Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The compound (I) of the present invention has much advantage, such as more selective inhibitory activity of COX-II, stronger activity, more suitable half-life, decreased adverse effect, or the like, compared to the known pyrazole compounds shown in the prior arts.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the compound (I) are shown in the following.

COX-I and COX-II activity in vitro:

(i) Test Method:

a. Preparation of the recombinant cyclooxygenase (COX)

The human cyclooxygenase COX-I and COX-II were expressed in transfected Chinese hamster ovary (CHO) cells. Monolayer cultures of semi-confluent CHO cells stably expressing COX-I and COX-II were washed twice and scraped into phosphate buffered saline (PBS). The cells were centrifuged at 200 x g for 5 minutes and the cell pellet was sonicated in reaction buffer containing 100 mM Tris-HCl (pH 7.4), 2  $\mu$ M hematin and 5 mM tryptophan. Broken cells were centrifuged for 5 minutes at 1700 x g at 4°C and the supernatants were used as crude



enzymes.

Cyclooxygenase activities in the absence or presence of inhibitors were measured by determining the level of prostaglandin  $E_2$  ( $PGE_2$ ) synthesis from arachidonic acid. Enzymes (1  $\mu$ g for COX-I and/or 3  $\mu$ g for COX-II) in a total volume of 200  $\mu$ l of reaction buffer were incubated in the absence and presence of various concentrations of inhibitors for 5 minutes at 30°C. The reaction was then started by the addition of arachidonic acid to the final concentration of 10  $\mu$ M. The reaction was terminated by 50  $\mu$ l of HCl (1N) after incubation at 30°C for 5 minutes.

$PGE_2$  was extracted with ethyl acetate, concentrated under a stream of nitrogen and analyzed by a radio immunoassay kit (Amersham) according to the manufacture's instructions.

b. Assay for human recombinant COX-I and COX-II activity

COX activity was assayed as  $PGE_2$  formation using radioimmunoassay to detect the prostaglandin release. The appropriate COX enzyme was incubated in 0.1 M Tris-HCl buffer (pH 7.3) containing hematin and tryptophan with the addition of arachidonic acid (10  $\mu$ M) for 5 minutes at 37°C. Compounds were pre-incubated with the enzyme for 5 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after 5 minutes at 37°C by addition of 20  $\mu$ l of 1N HCl.  $PGE_2$  formation was measured by radioimmunoassay (Amersham).

(ii) Test Results : COX-I and COX-II activity in vitro :

Test compound (Example No.)	Human COX-II $IC_{50}$ ( $\mu$ M)	Human COX-I $IC_{50}$ ( $\mu$ M)
5	$\leq 1$	>100
3	$\leq 1$	>100
12	$\leq 1$	>100

The compound (I) and a pharmaceutically acceptable salt thereof, are used as a medicament by intravenous, intracutaneous,

intramuscular, pulmonary, or oral administration, or insufflation to human beings or animals.

A pharmaceutical composition of the present invention is a homogeneous mixture which comprises one of the compounds (I) or pharmaceutically acceptable salts thereof, as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition is manufactured by mixing the sufficient amount of the compound (I) or a salt thereof as an active ingredient with a pharmaceutically non-toxic carrier or excipient to give homogeneous mixture. The pharmaceutically non-toxic carriers and excipients may be organic or inorganic and solid or liquid, and can be any of the conventional ones suitable for oral, parenteral or external (topical) administration.

For therapeutic purpose, the pharmaceutical composition of the present invention can be used in a form of a pharmaceutical preparation, for example, in a solid, semisolid, or liquid form. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

In the pharmaceutical composition the compound (I) or a pharmaceutically acceptable salt thereof is included in an sufficient amount to have the desired effects of aforementioned pharmaceutical activities on the aforesaid diseases in human beings or animals.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered

per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

#### Preparation 1

A mixture containing 1-[4-(methylthio)phenyl]-4,4,4-trifluorobutane-1, 3-dione (8.0 g), (3-chloro-4-methoxy)phenylhydrazine hydrochloride (6.4 g) and acetic acid (45 ml) was stirred at 100-110°C. After 3 hours, the reaction mixture was concentrated in vacuo. The resultant residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave an oil (11.5 g). The obtained product was used for next reaction without purification.

This oil was dissolved in dichloromethane (100 ml), and 3-chlorobenzoic acid (80%, 5.92 g) was added to this solution over a period of 15 minutes at an ice-bath temperature. After being stirred for 1 hour, the reaction mixture was diluted with dichloromethane (50 ml) and then washed with aqueous sodium carbonate solution (40 ml x 2) and brine. The organic layer was dried over  $\text{MgSO}_4$  and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate to give 1-(3-chloro-4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole (8.95 g) in 71% yield.

IR (KBr) : 1505, 1270, 1235, 1160, 1135, 1050  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.76(3H,s), 3.93(3H,s), 6.80-7.67(8H,m)

MASS : 415(M+1)

#### Preparation 2

A mixture of tert-butyl nitrite (2.6 ml) and copper (II) chloride (2.3 g) in acetonitrile (25 ml) was heated at 60-65°C for 30 minutes. After the reaction mixture was cooled to room temperature, 3-amino-1-(3-chloro-4-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazole (5.0 g) was

added to the mixture, and then the resulting mixture was stirred for 1.5 hours and concentrated in vacuo. The residue was partitioned between aqueous 10% hydrochloric acid solution and ethyl acetate. The organic layer was separated and washed with brine. The evaporation of the solvent followed by column chromatography on silica gel eluting with dichloromethane gave 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazole (3.1 g) in 58% yield. This product was oxidized by using 3-chloroperbenzoic acid, followed by an usual work-up, to give 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole (2.6 g) in 80% yield.

IR (KBr) : 1505, 1375, 1270, 1055  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.75(3H,s), 3.92(3H,s), 6.49(1H,s), 6.82- 7.65(7H,m)

MASS : 381(M+1)

#### Preparation 3

A mixture of methyl 4-(4-methylthiophenyl)-2,4-dioxobutanoate (5.0 g) and (4-chloro-3-methoxy)phenylhydrazine hydrochloride (5.2 g) in dioxane (30 ml) and ethanol (30 ml) was stirred at reflux temperature for 3 hours. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate to give methyl {1-(4-chloro-3-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazol-3-yl}carboxylate (6.4 g) in 83.0% yield.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.49(3H,s), 3.75(3H,s), 3.98(3H,s), 6.75-7.33(8H,m)

MASS : 389(M+1)

#### Preparation 4

To methyl {1-(4-chloro-3-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazol-3-yl}carboxylate (6.3 g) in formamide (35 ml) was added sodium methoxide (920 mg), and the resulting mixture was heated at 100°C under a nitrogen atmosphere. After 40 minutes the reaction mixture was cooled in an ice bath, and the resulting precipitates were collected by filtration and washed with ethyl acetate to give the desired

pyrazole amide (4.18 g). The amide was added to Vilsmeier reagent, prepared from N,N-dimethylformamide (15 ml) and phosphorus oxychloride (1.8 ml), at 5°C and then the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water, and the resulting precipitates were collected by filtration and dried at 50°C for 4 hours to afford the desired pyrazole nitrile (4.1 g). To this nitrile in dichloromethane (40 ml) was added by portions 3-chloroperbenzoic acid (2.84 g) at an ice-bath temperature. After being stirred at the same temperature for 2 hours, the reaction mixture was diluted with dichloromethane (50ml) and washed successively with aqueous sodium carbonate solution and brine, and dried over magnesium sulfate. The evaporation of the solvent gave 1-(4-chloro-3-methoxyphenyl)-3-cyano-5-[4-(methylsulfinyl)phenyl]pyrazole (4.16 g) in 69.1% yield.

IR (KBr) : 2235, 1590, 1285, 1075  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.76(3H,s), 3.82(3H,s), 6.66-7.68(8H,m)

MASS : 372(M+1)

#### Preparation 5

1-(4-Fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Preparation 1.

IR (Neat) : 1605, 1245, 1160, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.76(3H), 6.82(1H,s), 7.03-7.67(7H,m)

MASS: 369(M+1)

#### Preparation 6

To a solution of 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-[4-(acetoxymethylsulfonyl)phenyl]pyrazole (2.0 g) in tetrahydrofuran(12 ml) and methanol (6 ml) was added aqueous 1N NaOH solution (4.8 ml) at an ice-bath temperature. After 15 minutes, the reaction mixture was allowed to warm to room temperature. After 30 minutes the reaction mixture was concentrated under reduced pressure to give sodium 4-[3-

chloro-1-(3-chloro-4-methoxyphenyl)pyrazol-5-yl]benzenesulfinate (1.8 g) as a powder.

IR (KBr) : 3400, 1505, 1370, 1265  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 3.87(3H,s), 6.76(1H,s), 7.08-7.51(7H,m)

#### Preparation 7

Sodium 4-[1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 6.

IR (KBr) : 1645, 1510, 1235, 1135  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 3.89(3H,s), 7.15-7.58(8H,m)

#### Preparation 8

Sodium 4-[1-(4-fluorophenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 6.

#### Preparation 9

Sodium 4-[1-(4-chloro-3-methoxyphenyl)-3-cyanopyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 6.

IR (KBr) : 2240, 1595, 1490, 1235  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 3.77(3H,s), 6.79-7.51(8H,m)

#### Preparation 10

A mixture of 1-[4-(methylthio)phenyl]-4,4,4-trifluoro-butane-1,3-dione (2.5 g) and 3-chlorophenylhydrazine hydrochloride (2.1 g) in acetic acid (20 ml) was stirred at 120°C for 1.5hr. The reaction mixture was cooled to room temperature and evaporated under reduced pressure.

The residue was partitioned between ethyl acetate and water. The organic layer was separated, and washed successively with saturated sodium carbonate solution and brine, dried over magnesium sulfate. The evaporation of the solvent gave 1-(3-chlorophenyl)-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole (3.8 g).

#### Preparation 11.

To a solution of 1-(3-chlorophenyl)-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole (3.8 g) in methylene chloride (40 ml) was added m-chloroperbenzoic acid (2.34 g; 70% purity) at 0-5°C with ice-water bath. After being stirred for 1 hour, the reaction mixture was washed with saturated sodium carbonate solution and brine, and dried over magnesium sulfate. The evaporation of the solvent gave 1-(3-chlorophenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole (3.76 g)

#### Preparation 12

To a solution of 5-[4-(acetoxymethylsulfonyl)phenyl]-1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazole (3.05 g) in methanol (75 ml) and tetrahydrofuran (15 ml) was added 1N-NaOH solution (3.9 ml) at room temperature. After being stirred for 30 minutes, the reaction mixture was evaporated under reduced pressure. The residue was triturated with ethanol to give sodium 4-[1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate (1.44 g).

#### Preparation 13

3-Chloro-1-(4-methylphenyl)-5-[4-(methylthio)phenyl]pyrazole (2.8 g) was dissolved in dichloromethane (30 ml) and cooled with an ice.

Meta-chloroperbenzoic acid (1.69 g) was added portionwise to this solution. After stirred for 1 hour, the reaction mixture was quenched with aqueous sodium thiosulfate solution. The aqueous layer was separated, and the organic layer was washed with aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate. After evaporation of the solvent, the obtained residue was triturated with isopropyl ether to give a powder, 3-chloro-1-(4-methylphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole (2.69 g).

NMR (DMSO- $d_6$ ,  $\delta$ ); 2.33 (3H, s), 2.75 (3H, s), 6.89 (1H, s), 7.18 (2H, d,  $J=8.4$  Hz), 7.25 (2H, d,  $J=8.4$  Hz),

7.43 (2H, d,  $J=8.4$  Hz), 7.67 (2H, d,  $J=8.4$  Hz).

IR (KBr): 3464, 3429, 3116, 1041, 2993, 2912  $\text{cm}^{-1}$ .

Mass  $m/e$  : 331 ( $M+1$ ).

#### Preparation 14

To a solution of 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-methylphenyl)pyrazole (2.65 g) in tetrahydrofuran (20 ml) was added 1N NaOH (6.54 ml) at room temperature. After stirred for 1 hour, the reaction mixture was concentrated under reduced pressure. The obtained residue was partitioned between ethyl ether (20ml) and water (20ml). The aqueous phase was separated and concentrated under reduced pressure to give a powder, which was washed with isopropyl ether (20 ml) and collected by filtration, giving 4-[3-chloro-1-(4-methylphenyl)pyrazol-5-yl]benzenesulfinate (2.34 g).

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.32 (3H, s), 6.75 (1H, s), 7.13-7.25 (6H, m), 7.48 (2H, d,  $J=8.1$  Hz).

IR (KBr): 3639, 3535, 3396, 3128, 1664, 1604  $cm^{-1}$ .

Mass  $m/e$  : 333 ( $M+$ ).

#### Preparation 15

Sodium 4-[3-chloro-1-(4-isopropenylphenyl)pyrazol-5-yl]benzenesulfinate was prepared according to a similar manner to that of Preparation 14.

IR (KBr) : 1645, 1565, 1550, 1515, 1375  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.10(3H, s), 5.15(1H, m), 5.50(1H, m), 6.76(1H, s), 7.16-7.58(8H, m)

#### Preparation 16

1-(4-Methylphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

IR (KBr) : 1510, 1465, 1275, 1235, 1160, 1125  $cm^{-1}$

#### Preparation 17

Sodium 4-[1-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 21, Example 22 and Preparation 14.



IR (KBr) : 1645, 1510, 1280, 1235, 1160, 1130  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.34(3H, s), 7.14-7.44(9H, m)

#### Preparation 18

1-(4-Methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)-pyrazole was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

IR (Neat) : 1510, 1465, 1240, 1160, 1130, 1100  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.75(3H, s), 3.86(3H, s), 6.80-7.63(9H, m).

MASS : 381( $M^+ + 1$ )

#### Preparation 19

Sodium 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 19, Example 20 and Preparation 12.

IR (KBr) : 1615, 1510, 1465, 1240, 1165, 1130  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.79(3H, s), 6.98-7.44(9H, m)

#### Preparation 20

Sodium 4-[1-(3-chloro-4-methylphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 20 and Preparation 12.

IR (KBr) : 3365, 1500, 1270, 1235, 1160, 1130  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.36(3H, s), 7.11-7.53(8H, m)

#### Preparation 21

1-(4-Fluoro-3-methylphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

IR (Neat) : 1500, 1230, 1160, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.28(3H, s), 2.75(3H, s), 6.81(1H, s), 6.96-7.77(7H, m).

MASS : 383( $M^+ + 1$ )

#### Preparation 22

Sodium 4-[1-(4-fluoro-3-methylphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example

19, Example 20 and Preparation 12.

IR (KBr) : 1590, 1575, 1502, 1460, 1415, 1250, 1165  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.25(3H, s), 7.06-7.59(8H, m)

#### Preparation 23

1-(3-Methylphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)-pyrazole was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

IR (Neat) : 1240, 1160, 1130, 1090  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.35(3H, s), 2.78(3H, s), 6.81(1H, s), 6.81-7.63(8H, m).

MASS : 365( $\text{M}^+$ +1)

#### Preparation 24

Sodium 4-[1-(3-methylphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 19, Example 20 and Preparation 12.

IR (KBr) : 1615, 1465, 1275, 1240, 1160, 1130  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.33(3H, s), 6.99-7.44(9H, m)

#### Preparation 25

1-(3-Fluoro-4-methylphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

IR (KBr) : 1685, 1505, 1460, 1270, 1245, 1160, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.30(3H, s), 2.76(3H, s), 6.80(1H, s), 6.92-7.66(7H, m).

MASS : 383( $\text{M}^+$ +1)

#### Preparation 26

Sodium 4-[1-(3-fluoro-4-methylphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 19, Example 20 and Preparation 12.

IR (KBr) : 1590, 1240, 1165, 1125  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.26(3H, s), 7.02-7.47(8H, m)

#### Preparation 27

1-(3-Chloro-4-methoxyphenyl)-5-(4-methylsulfinyl-3-fluorophenyl)-3-

(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Preparation 10.

mp : 117-119°C

IR (KBr) : 1500, 1270, 1225, 1155, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.52(3H, s), 3.93(3H, s), 6.73-7.47(7H, m).

MASS : 417( $\text{M}^+ + 1$ )

#### Preparation 28

Sodium 2-fluoro-4-[1-(4-methoxy-3-chlorophenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 20 and Preparation 12.

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 3.90(3H, s), 6.97-7.62(7H, m)

#### Preparation 29

1-(4-Chloro-3-methylphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

IR (Neat) : 1475, 1405, 1265, 1235, 1160, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.37(3H, s), 2.75(3H, s), 6.81(1H, s), 6.91-7.77(7H, m).

MASS : 399( $\text{M} + 1$ )

#### Preparation 30

Sodium 4-[1-(4-chloro-3-methylphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 19, Example 20 and Preparation 12.

IR (KBr) : 1610, 1475, 1270, 1240, 1160, 1135  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 2.34(3H, s), 7.04-7.52(8H, m)

#### Preparation 31

Sodium 4-[1-(4-isopropenylphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 20 and Preparation 12. The obtained compound could not be characterized by its spectroscopic data because of containing some by-products and the crude was used for the next reaction without purification.

#### Preparation 32

1-(3-Methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)-pyrazole was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

IR (Neat) : 1600, 1490, 1465, 1280, 1250, 1215, 1160  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.75(3H, s), 3.76(3H, s), 6.78-8.13(9H, m).

MASS : 381( $\text{M}^+ + 1$ )

#### Preparation 33

Sodium 4-[1-(3-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]-benzenesulfinate was prepared by a similar procedure to that of Example 19, Example 20 and Preparation 12.

IR (KBr) : 1605, 1490, 1465, 1435, 1280, 1250, 1220, 1165, 1130  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 3.72(3H, s), 6.82-7.62(9H, m)

#### Preparation 34

Sodium 4-[1-(4-isopropylphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 20 and Preparation 12.

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.21(6H, d,  $J=7.0\text{Hz}$ ), 2.87-3.01(1H, m), 7.14-7.44(9H, m)

#### Preparation 35

1-(3-Cyano-4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

mp : 148-150°C

IR (KBr) : 2235, 1505, 1285, 1235, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.77(3H, s), 3.98(3H, s), 6.82(1H, s), 6.95-7.69(7H, m).

MASS : 406( $\text{M}^+ + 1$ )

#### Preparation 36

Sodium 4-[1-(3-cyano-4-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 12.

IR (KBr) : 2230, 1645, 1505, 1280  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.95(3H, s), 7.17-7.93(8H, m).

#### Preparation 37

Sodium 4-[1-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 6.

IR (KBr) : 1500, 1450, 1270, 1170  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.88(3H, s), 6.82-7.33(9H, m).

#### Preparation 38

Sodium 4-[1-(4-bromo-3-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar manner to that of Example 20 and preparation 12.

IR (KBr) : 1590, 1475, 1405, 1255, 1225, 1160  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.75(3H, s), 6.73-7.64(8H, m).

#### Preparation 39

Sodium 4-[1-(4-methoxyphenyl)-3-(difluoromethyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 6.

IR (KBr) : 3401, 3268, 1616, 1512, 1247, 1033  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.78(3H, s), 6.82-7.44(9H, m).

#### Preparation 40

1-(3-Bromophenyl)-3-chloro-5-[4-(methylthio)-phenyl]pyrazole was prepared by the treatment of 4-methylthiocinnamionitrile with 3-bromophenylhydrazine hydrochloride followed by dehydrogenation with  $\text{MnO}_2$ , and chlorination via the corresponding diazonium salt as described in Preparation 2.

IR (Neat) : 1590, 1480, 1370, 1235, 1095  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.49(3H, s), 5.77(1H, s), 7.09-7.59(8H, m).

MASS : 379( $\text{M}^+$ )

#### Preparation 41

Sodium 4-[1-(3-bromophenyl)-3-chloropyrazol-5-yl]benzenesulfinate was prepared by a similar manner to that of Preparation 14.

IR (KBr) : 3375, 3140, 1585, 1475, 1370, 1240  $\text{cm}^{-1}$

#### Preparation 42

Sodium 4-[1-(3-fluoro-4-methylphenyl)-3-chloropyrazol-5-yl]-benzenesulfinate was prepared by a similar procedure to that of Preparation 6.

IR (KBr) : 1590, 1505, 1370  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.24(3H, s), 6.77(1H, s), 6.92-7.68(7H, m).

#### Preparation 43

Sodium 4-[1-(4-fluoro-3-methylphenyl)-3-chloropyrazol-5-yl]-benzenesulfinate was prepared by a similar procedure to that of Preparation 6.

IR (KBr) : 3375, 1500, 1375, 1230  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.23(3H, s), 6.77(1H, s), 7.03-7.44(7H, m).

#### Preparation 44

This starting material was prepared by the treatment of 4-methylthiocinnamionitrile and 4-chloro-3-methylphenylhydrazine hydrochloride followed by dehydrogenation with  $\text{MnO}_2$ , which was converted to 3-chloro-1-(4-chloro-3-methylphenyl)-5-[4-(methylthio)phenyl]pyrazole by using a similar manner described in Preparation 2.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.38(3H, s), 2.48(3H, s), 6.40(1H, s), 6.90(1H, dd,  $J=8.5$  and 2.6Hz), 7.10-7.31(6H, m).

MASS : 349 ( $\text{M}^+$ )

#### Preparation 45

Sodium 4-[3-chloro-1-(4-chloro-3-methylphenyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Example 22 and Preparation 14.

#### Preparation 46

Sodium 4-[3-chloro-1-(3-chloro-4-methylphenyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 13, Example 21, Example 22 and Preparation 14.

#### Preparation 47

3-Chloro-1-(3-methylphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole was obtained from 3-chloro-1-(3-methylphenyl)-5-[4-(methylthio)-phenyl]pyrazole in the similar manner that of Preparation 13.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.30(3H, s), 2.75(3H, s), 6.90(1H, s), 6.98-7.02(1H, m), 7.22-7.34(3H, m), 7.44(2H, d,  $J=8.3\text{Hz}$ ), 7.67(2H, d,  $J=8.3\text{Hz}$ ).

IR (KBr) : 3120, 3049, 2989, 2910  $\text{cm}^{-1}$ .

Mass  $m/e$  : 331 ( $M^+ + 1$ ).

#### Preparation 48

Sodium 4-[3-chloro-1-(3-methylphenyl)pyrazol-5-yl]benzenesulfinate was obtained from 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-methylphenyl)pyrazole in the similar manner that of Preparation 14.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.31(3H, s), 6.77(1H, s), 6.93-6.96(1H, m), 7.17-7.32(5H, m), 7.43(2H, d,  $J=8.1\text{Hz}$ ).

IR (KBr) : 3623, 3396, 3363, 3059, 1668, 1616  $\text{cm}^{-1}$ .

Mass  $m/e$  : 333 ( $M^+ + 1$ ).

#### Preparation 49

3-Chloro-1-(3-chlorophenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole was prepared by a similar procedure to that of Preparation 13.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.75(3H, s), 6.51(1H, s), 7.05(1H, dt,  $J=8.2\text{Hz}$ ), 7.28-7.41(3H, m), 7.39(2H, d,  $J=8\text{Hz}$ ), 7.64(2H, d,  $J=8\text{Hz}$ ).

IR (KBr) : 1047  $\text{cm}^{-1}$

Mass( $m/z$ ) : 351( $M+1$ )

#### Preparation 50

Sodium 4-[3-chloro-1-(3-chlorophenyl)pyrazol-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 14.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 6.80(1H, s), 7.13-7.25(4H, m), 7.24-7.47(4H, m),

IR (KBr) : 1621  $\text{cm}^{-1}$

mass ( $m/z$ ) : 351( $M$ )

#### Preparation 51

3-Chloro-1-(4-chlorophenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole was prepared by a similar procedure to that of Preparation 13.

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.76(3H, s), 6.50(1H, s), 7.20(2H, d, J=8.8Hz), 7.33(2H, d, J=9Hz), 7.37(2H, d, J=8Hz), 7.63(2H, d, J=8Hz).

IR (KBr) : 1049 cm<sup>-1</sup>

mass (m/z) : 351(M+1)

#### Preparation 52

Sodium 4-[3-chloro-1-(4-chlorophenyl)pyrazole-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 14.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 6.79(1H, s), 7.20(2H, d, J=8Hz), 7.29(2H, d, J=9Hz), 7.44(2H, d, J=8Hz), 7.50(2H, d, J=9Hz).

IR (KBr) : 1617 cm<sup>-1</sup>

mass (m/z) : 351(M)

#### Preparation 53

Sodium 4-[3-chloro-1-(4-fluorophenyl)pyrazole-5-yl]benzenesulfinate was prepared by a similar procedure to that of Preparation 14.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 6.79(1H, s), 7.20(2H, d, J=8Hz), 7.24-7.39(4H, m), 7.45(2H, d, J=8Hz).

IR (KBr) : 1654 cm<sup>-1</sup>

mass (m/z) : 335(M)

#### Preparation 54

5-(4-Methylphenyl)-1-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazol was prepared by a similar procedure to that of Preparation 10 and Preparation 11.

#### Preparation 55

Sodium 4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfinate was prepared by a similar procedure to that of Example 19, Example 20 and Preparation 12.

IR (Neat) : 1645, 1565, 1465, 1235, 1135 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, d) : 2.29(3H, s), 7.12-7.64(9H, m).

#### Example 1

A mixture containing 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-[(methylsulfinyl)phenyl]pyrazole (2.5 g), sodium acetate (2.0 g) and



acetic anhydride (30 ml) was stirred at reflux temperature for 4 hours. The reaction mixture was cooled and the insoluble materials were removed by filtration. Toluene (50 ml) was added to the filtrate and then the mixture was concentrated under reduced pressure. To the residue was added toluene (50 ml), and again the reaction mixture was evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with dichloromethane to give 5-[(acetoxymethylsulfinyl)phenyl]-3-chloro-1-(3-chloro-4-methoxyphenyl)-pyrazole as a synthetic intermediate. To the intermediate in a mixed solvent of dichloromethane (20 ml) and methanol (10 ml) was added magnesium monoperoxyphthalate (6.8 g) with stirring at an ice-bath temperature. After the addition was completed, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with dichloromethane (100 ml) and then washed successively with water, aqueous sodium carbonate solution and brine, and dried over  $\text{MgSO}_4$ . The evaporation of the solvent gave a gummy oil, which was crystallized in ethanol and collected by filtration to give 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-chloro-4-methoxyphenyl)pyrazole (2.4 g) in 80.3% yield. The analytical sample was obtained by recrystallization from ethanol.

IR (KBr) : 1760, 1505, 1320, 1150, 1060  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.08(3H,s), 3.92(3H,s), 5.16(2H,s), 6.55(1H,s), 6.84-7.92(7H,m)

MASS : 455(M)

Anal. Calcd for  $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_5\text{S}$  : C, 50.12 ; H, 3.54 ; N, 6.15

Found : C, 49.51 ; H, 3.41 ; N, 6.08

mp : 139-140°C

#### Example 2

5-[4-(Acetoxymethylsulfonyl)phenyl]-1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole was prepared by a similar procedure

to that of Example 1.

IR (KBr) : 1745, 1505, 1270, 1205, 1155, 1125  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.09(3H), 3.94(3H,s), 5.16(2H,s), 6.87-7.94(8H,m)

MASS : 489(M+1)

mp : 86 - 88°C

### Example 3

A mixture of sodium 4-[1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate (200 mg) and 3-bromopropanol (82 mg) in N,N-dimethylformamide (0.5 ml) was heated at 100°C for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . The evaporation of the solvent gave a gummy oil, which was purified by column chromatography on silica gel with eluting a mixed solvent of ethyl acetate and n-hexane (2 : 1) to give 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (65 mg) as a powder.

IR (Neat) : 3480, 1500, 1275, 1230, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.88-2.05(3H,m), 3.23-3.79(4H,m), 3.94(3H,s), 6.84-7.93(8H,m)

MASS : 475(M+1)

### Example 4

3-Chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 3. Purification by column chromatography on silica gel eluting with ethyl acetate followed by trituration in ethanol gave the desired product as a powder.

IR (KBr) : 3505, 1505, 1310, 1270, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.62(1H,t,J=6.0Hz), 3.35-4.07(4H,m), 3.93(3H,s), 6.53(1H,s), 6.84-7.93(7H,m)

MASS : 427(M+1)

### Example 5

1-(3-Chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar manner to that of Example 3. After purification by column chromatography eluting with ethyl acetate, the desired product was obtained as a powder.  
IR (KBr) : 3440, 1665, 1500, 1275, 1230, 1140  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.61(1H,t,J=6.2Hz), 3.36-4.67(4H,m), 3.93(3H,s), 6.74-8.02(8H,m)  
MASS : 461(M+1)

#### Example 6

A mixture of sodium 4-[1-(3-chloro-4-methoxyphenyl)-3-(trifluoro-methyl)pyrazol-5-yl]benzenesulfinate (300 mg) and 2-chloroethyl methylsulfide (101 mg) in N,N-dimethylformamide (0.75 ml) was heated at 100°C in the presence of catalytic amount of potassium iodide. After 1.5 hours, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . The evaporation of the solvent gave a gummy oil, which was triturated with n-hexane to give 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-(methylthio)ethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (274 mg) as a powder.

IR (KBr): 1600, 1500, 1270, 1230, 1135  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.10(3H,s), 2.70-4.27(4H,m), 3.94(3H,s), 6.82-7.92(8H, m)  
MASS : 491(M+1)

Anal. Calcd for  $\text{C}_{20}\text{H}_{18}\text{ClF}_3\text{N}_2\text{O}_3\text{S}_2$  : C, 48.93 ; H, 3.69 ; N, 5.71

Found : C, 49.18 ; H, 3.68 ; N, 5.60

#### Example 7

A mixture of sodium 4-[1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate (200 mg) and 5-chloropentanol (73 mg) in N,N-dimethylformamide (0.5 ml) was heated at 100°C in the presence of potassium iodide as a catalyst. After 4 hours, the reaction mixture was poured into water and extracted with ethyl

acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . The evaporation of the solvent gave the residue, which was purified by column chromatography on silica gel eluting with ethyl acetate to afford 1-(3-chloro-4-methoxyphenyl)-5-{4-[(5-hydroxypentyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (186 mg) in 81.2% yield.

IR (Neat) : 3405, 1500, 1270, 1235, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.31-1.85(5H,m), 3.08-3.70(6H,m), 3.94(3H,s), 6.82-7.91 (8H,m)

MASS : 503(M+1)

#### Example 8

A mixture of sodium 4-[1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate (200 mg) and 4-chlorobutanol (64 mg) in N,N-dimethylformamide (0.5 ml) was heated at 100°C in the presence of potassium iodide as a catalyst. Additional 4-chlorobutanol and potassium carbonate were added to the reaction mixture. After 4 hours, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . The evaporation of the solvent gave the residue, which was purified by column chromatography on silica gel eluting with ethyl acetate to afford 1-(3-chloro-4-methoxyphenyl)-5-{4-[(4-hydroxybutyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (42 mg) in 18.8% yield.

IR (Neat) : 3430, 1505, 1275, 1235, 1140  $\text{cm}^{-1}$

MASS : 489(M+1)

#### Example 9

A mixture of sodium 4-[1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazol-5-yl]benzenesulfinate (300 mg) and ethyl bromoacetate (126 mg) in N,N-dimethylformamide (0.8 ml) was heated at 100°C for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . The evaporation of the solvent gave the residue,

which was purified by column chromatography on silica gel eluting with a mixed solvent of ethyl acetate and n-hexane (1:2) to afford 1-(3-chloro-4-methoxyphenyl)-5-[4-(ethoxycarbonylmethylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (200 mg) in 58.1% yield.

IR (KBr) : 1740, 1505, 1330, 1275, 1230, 1160  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.22(3H,t,J=7.0Hz), 3.92(3H,s), 4.11(2H,s), 4.16(2H,q,J=7.0Hz), 6.85-7.96(8H,m)

MASS : 503(M+1)

#### Example 10

To a stirred solution of 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (100 mg) and triethylamine (26 mg) in dichloromethane (5 ml) was added dropwise a solution of methanesulfonyl chloride (25 mg) in dichloromethane (0.5 ml) at an ice-bath temperature. After 40 minutes the reaction mixture was evaporated under reduced pressure. The residue was diluted with ethyl acetate and then filtered. The filtrate was evaporated under reduced pressure to afford the desired mesylate. To the mesylate in acetonitrile (5 ml) was added 40% aqueous methylamine solution (42 mg) at room temperature and the resulting mixture was stirred overnight. The reaction mixture was evaporated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, and dried over  $\text{MgSO}_4$ . The obtained residue was purified by column chromatography on silica gel eluting with a mixed solvent of ethyl acetate and methanol (10 : 1) to give 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-methylaminoethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (72 mg) as a powder.

IR (KBr) : 3405, 1605, 1505, 1315, 1275, 1230, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.05(1H,broad s), 2.46(3H,s), 3.07(2H,t,J=6.0Hz), 3.38(2H,t,J=6.0Hz), 3.94(3H,s), 6.85-7.93(8H,m)

MASS : 474(M+1)

#### Example 11

1-(3-Chloro-4-methoxyphenyl)-5-{4-[(2-aminoethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar manner to that of Example 10.

IR (KBr) : 3465, 1500, 1275, 1230, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.03(2H,t,J=6.0Hz), 3.25(2H,t,J=6.0Hz), 3.93(3H,s), 6.85-7.91(8H,m)

#### Example 12

A mixture of 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)-sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (70 mg) and acetic anhydride (0.5 ml) was heated at 150°C with stirring. After 2 hours, the reaction mixture was diluted with toluene (20 ml) and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with a mixed solvent of ethyl acetate and n-hexane (1 : 1) to give 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-acetoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (51 mg) as a powder.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.87(3H,s), 3.48(2H,t,J=6.0Hz), 3.94(3H,s), 4.41(2H,t,J=6.0Hz)

MASS : 503(M+1)

#### Example 13

3-Chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-acetoxyethyl)-sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 12.

IR (KBr) : 1745, 1505, 1380, 1310, 1245, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.87(3H,s), 3.47(2H,t,J=6.0Hz), 3.93(3H,s), 4.41(2H,t,J=6.0Hz), 6.52(1H,s), 6.84-7.91(7H,m)

MASS : 469(M-)

mp : 113 - 114°C

#### Example 14

To a solution of 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-(methylthio)ethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (150 mg) in

dichloromethane (5 ml) was added 3-chloroperoxybenzoic acid (70%, 201 mg) at room temperature for 2 days. The reaction mixture was partitioned between dichloromethane and water. The organic layer was separated and washed successively with aqueous sodium carbonate solution and brine, dried over  $\text{MgSO}_4$ . The evaporation of the solvent gave a gummy oil, which was purified by column chromatography on silica gel eluting a mixed solvent of dichloromethane and methanol (50 : 1), and then crystallized from ethanol to give 1-(3-chloro-4-methoxyphenyl)-5-{4-[[2-(methylsulfonyl)ethyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (100 mg) in 59% yield.

IR (KBr) : 3430, 1560, 1500, 1375, 1315, 1230, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.03(3H,d,10.0Hz), 3.36-4.52(4H,m), 3.94(3H,s), 6.87-7.94(8H,m)

MASS : 523(M+1)

#### Example 15

5-{4-[[Acetoxymethyl]sulfonyl]phenyl}-1-(4-fluorophenyl)-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 1.

IR (Neat) : 1770, 1605, 1335, 1240, 1200, 1155  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.08(3H,s), 5.17(2H,s), 6.88(1H,s), 7.00-7.95(7H,m)

MASS : 443(M+1)

#### Example 16

1-(4-Fluorophenyl)-5-{4-[[2-hydroxyethyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

IR (Neat) : 3502, 1605, 1315, 1280, 1245, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.56(1H,t,J=6.0Hz), 3.36-4.11(4H,m), 6.87(1H,s), 7.03-7.96(7H,m)

MASS : 415(M+1)

#### Example 17

5-{4-[[Acetoxymethyl]sulfonyl]phenyl}-1-(4-chloro-3-methoxy-

phenyl)-3-cyanopyrazole was prepared by a similar procedure to that of Example 1.

IR (KBr) : 2240, 1765, 1595, 1490, 1330, 1240, 1195, 1145  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.08(3H,s), 3.86(3H,s), 5.16(2H,s), 6.60-7.95(8H,m)

MASS : 446(M+1)

#### Example 18

1-(4-Chloro-3-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}-3-cyanopyrazole was prepared by a similar procedure to that of Example 3.

IR (KBr) : 3500, 2240, 1590, 1485, 1305, 1235, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.52(1H,t,J=6.0Hz), 3.36-4.10(4H,m), 3.85(1H,s), 6.61-7.97(8H,m)

MASS : 418(M+1)

Anal. Calcd for  $\text{C}_{19}\text{H}_{16}\text{ClN}_3\text{O}_4\text{S}$  : C, 54.61 ; H, 3.86 ; N, 10.06

Found : C, 54.36 ; H, 3.80 ; N, 9.98

#### Example 19

A mixture of 1-(3-chlorophenyl)-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole (3.7 g) and sodium acetate (2.9 g) in acetic anhydride (20 ml) was refluxed for 4 hours. The reaction mixture was cooled to room temperature, and insoluble were removed by filtration and washed with toluene. The filtrates were evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and washed with saturated sodium carbonate solution and brine, and dried over magnesium sulfate. The evaporation of the solvent gave 5-[4-(acetoxymethylthio)phenyl]-1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazole (3.6 g).

#### Example 20

To a solution of 5-[4-(acetoxymethylthio)phenyl]-1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazole (3.6 g) in methylene chloride (20 ml) and methanol (13 ml) was added magnesium monoperoxyphthalate (7.3 g) at 0-5°C with ice-water bath. After being stirred at



room temperature for 1 hour, the reaction mixture washed successively with saturated sodium carbonate solution and brine dried over magnesium sulfate. After evaporation of the solvent, the residue was triturated with isopropyl alcohol to give 5-[4-(acetoxymethylsulfonyl)-phenyl]-1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazole (3.05 g).

#### Example 21

To a stirred solution of 3-chloro-1-(4-methylphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole (2.65 g) in acetic anhydride (19 ml) was added sodium acetate (2.43 g) portionwise. After stirred for 3 hour at 180°C, the reaction mixture was cooled to room temperature and then filtered. The filter cake was washed with toluene (20 ml). The filtrate and the washing were combined and concentrated under reduced pressure. The resulting residue was partitioned between ethyl acetate (30 ml) and water (30 ml). The organic layer was washed successively with aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. After evaporation of the solvent, the obtained residue was purified by column chromatography on silicagel eluting with a mixed solvent of ethyl acetate and n-hexane. The fractions containing a desired product were collected and then concentrated under reduced pressure to give 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-methylphenyl)pyrazole (2.89 g).

NMR (DMSO-d<sub>6</sub>,  $\delta$ ); 2.05 (3H, s), 2.33 (3H, s), 5.53 (2H, s), 6.80 (1H, s), 7.15-7.26 (6H, m), 7.42 (2H, d, J=8.5 Hz).

IR (Neat): 3473, 3134, 3035, 2964, 2927, 2873, 1747, 1601 cm<sup>-1</sup>.

Mass m/e : 373 (M++1).

#### Example 22

A stirred solution of 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-methylphenyl)pyrazole (2.81 g) in methanol (10 ml) and dichloromethane (10 ml) was cooled with an ice. Monoperoxyphthalic acid magnesium salt (5.95 g) was added portionwise to this solution. After 1 hour the reaction mixture was poured into a mixture of water (20

ml) and dichloromethane (20 ml). The organic layer was separated and washed successively with aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. Evaporation of the solvent followed by triturating the resulting residue with isopropyl ether gave 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-methylphenyl)-pyrazole (2.71 g).

NMR (DMSO- $d_6$ ,  $\delta$ ); 2.04 (3H, s), 2.34 (3H, s), 5.44 (2H, s), 6.98 (1H, s), 7.17 (2H, d,  $J=8.5$  Hz), 7.25 (2H, d,  $J=8.5$  Hz), 7.53 (2H, d,  $J=8.5$  Hz, 1.8 Hz) 7.89 (2H, dt,  $J=8.5$  Hz, 1.8 Hz)

IR (KBr): 3126, 3072, 3041, 2993, 2929, 1768  $\text{cm}^{-1}$ .

Mass  $m/e$  : 405 ( $M+1$ ).

#### Example 23

To a stirred solution of 3-chloro-1-(4-acetylphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole (1.0 g) in tetrahydrofuran (50 ml) was dropwise 1.14 N methyllithium diethyl ether solution (5 ml) at an ice-bath temperature under a nitrogen atmosphere. After the addition was completed, the reaction mixture was allowed to react at room temperature overnight. Aqueous ammonium chloride solution was added to the mixture at an ice-bath temperature. Extraction with ethyl acetate followed by washing with brine and evaporation under reduced pressure gave an oil, which was purified by a column chromatography on silica gel eluting with dichloromethane-methanol (50 : 1) to afford the desired alcohol. This alcohol was dissolved in benzene (10ml), and thionyl chloride (0.3 ml) and pyridine (2 ml) were added. The resulting mixture was heated at 150°C with stirring for 1 hour, and then poured into water. Extraction with ethyl acetate followed by washing with aqueous dilute hydrochloric acid solution and brine, and evaporation under reduced pressure gave a crude product, which was subjected to a column chromatography on silica gel eluting with dichloromethane-n-hexane (3 : 1) to give 3-chloro-1-(4-isopropenylphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole (346 mg) in 50% yield.

IR (KBr) : 1600, 1510, 1470, 1430, 1365, 1090  $\text{cm}^{-1}$

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.14(3H, s), 2.48(3H, s), 5.13(1H, m), 5.40(1H, m), 6.40(1H, s), 7.10-7.45(8H, m).

MASS : 341(M<sup>+</sup>+1)

#### Example 24

5-[(4-(Acetoxymethylthio)phenyl]-3-chloro-1-(isopropenylphenyl)-pyrazole was prepared according to a similar manner to that of Preparation 13 and Example 21.

IR (Neat) : 1745, 1515, 1375, 1210 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.11(3H, s), 2.14(3H, s), 5.13(1H, m), 5.40(1H, m), 5.44(2H, s), 6.43(1H, s), 7.16-7.46(8H, m).

MASS : 399(M<sup>+</sup>+1)

#### Example 25

3-Chloro-1-(4-isopropenylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 3.  
mp : 158-161°C

IR (KBr) : 1510, 1375, 1305, 1150, 1110 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.15(3H, s), 3.21(3H, s), 3.39(1H, t, J=6.0Hz), 3.76(2H, t, J=6.0Hz), 5.15(1H, m), , 5.40(1H, m), 6.53(1H, s), 7.17-7.89(8H, m).

MASS : 417(M<sup>+</sup>+1)

Anal. Calcd for C<sub>21</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>S 1/3H<sub>2</sub>O : C, 59.64; H, 5.16; N, 6.62.

Found : C, 59.72; H, 4.98; N, 6.60.

#### Example 26

3-Chloro-1-(4-isopropenylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 3.

mp : 122-125°C

IR (KBr) : 3465, 3435, 1510, 1370, 1305, 1275, 1235, 1130 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.15(3H, s), 3.35-4.19(4H, m), 5.16(1H, m), 5.41(1H, m), 6.51-7.91(9H, m).

MASS : 403(M<sup>++</sup>+1)

Anal Calcd for C<sub>20</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>S : C, 58.74; H, 4.85; N, 6.85.

Found : C, 58.87; H, 4.69; N, 6.80.

#### Example 27

1-(4-Methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 102-104°C

IR (KBr) : 3480, 1510, 1465, 1280, 1235, 1155, 1120  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.40(3H, s), 2.63(1H, t,  $J=6.0\text{Hz}$ ), 3.34-4.19(4H, m), 6.82-7.91(9H, m).

MASS : 411( $\text{M}^++1$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3\text{S}$  : C, 55.61; H, 4.17; N, 6.82.

Found : C, 55.06 ; H, 4.09 ; N, 6.71.

#### Example 28

1-(4-Methylphenyl)-5-{4-[(3-acetoxypentyl)sulfonyl] phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 95-96°C

IR (KBr) : 1735, 1285, 1235, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.03-2.16(2H, m), 2.08(3H, s), 2.40(3H, s), 3.14-3.22(2H, m), 4.13(2H, t,  $J=6.0\text{Hz}$ ), 6.85(1H, s), 7.13-7.89(8H, m).

MASS : 467( $\text{M}^++1$ )

Anal. Calcd for  $\text{C}_{22}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_4\text{S}$  : C, 56.56; H, 4.54; N, 6.00

Found :C, 56.73; H, 4.56; N, 5.94.

#### Example 29

1-(4-Methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 96-98°C

IR (KBr) : 3545, 3480, 1605, 1525, 1315, 1270, 1235, 1165, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.61(1H, t,  $J=6.0\text{Hz}$ ), 3.37(2H, t,  $J=6.0\text{Hz}$ ), 3.84(3H, s), 4.03(2H, q,  $J=6.0\text{Hz}$ ), 6.85-7.91(9H, m).

MASS : 427(M<sup>+</sup>+1)

Anal. Calcd for C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>S : C, 53.52; H, 4.02; N, 6.57.

Found : C, 53.28 ; H, 3.99 ; N, 6.47.

#### Example 30

5-[4-(Acetoxymethylthio)phenyl]-3-trifluoromethyl-1-(3-chloro-4-methylphenyl)pyrazole was prepared by a similar method to that of Preparation 10, Preparation 11 and Example 19.

IR (KBr) : 1745, 1500, 1465, 1230, 1210, 1160, 1135 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 2.11(3H, s), 2.40(3H, s), 5.45(2H, s), 6.74(1H, s), 6.99-7.44(7H, m).

MASS : 441(M<sup>+</sup>+1)

#### Example 31

1-(3-Chloro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

IR (KBr) : 3495, 1500, 1315, 1275, 1235, 1135 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 2.41(3H, s), 2.59(1H, t, J=6.0Hz), 3.38(2H, t, J=6.0Hz), 4.04(2H, q, J=6.0Hz), 6.85(1H, s), 6.97-7.95(7H, m).

MASS : 445(M<sup>+</sup>+1)

#### Example 32

1-(3-Chloro-4-methylphenyl)-5-{4-[(2-acetoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 12 (S9803378).

mp : 105-108°C

IR (KBr) : 1740, 1500, 1465, 1395, 1325, 1235, 1150 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 1.87(3H, s), 2.41(3H, s), 3.48(2H, t, J=6.0Hz), 4.18(2H, t, J=6.0Hz), 6.82-7.93(8H, m).

MASS : 487(M<sup>+</sup>+1)

Anal. Calcd for C<sub>21</sub>H<sub>18</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>4</sub>S : C, 51.80 ; H, 3.73 ; N, 5.75.

Found : C, 51.94 ; H, 3.70 ; N, 5.67.

#### Example 33

1-(4-Fluoro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 80-83°C

IR (KBr) : 3480, 1500, 1310, 1280, 1230, 1115  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.28(3H, s), 2.58(1H, t,  $J=6.0\text{Hz}$ ), 3.37(2H, t,  $J=6.0\text{Hz}$ ), 4.03(2H, q,  $J=6.0\text{Hz}$ ), 6.85(1H, s), 6.97-7.94(7H, m).

MASS : 429( $M^++1$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{16}\text{F}_4\text{N}_2\text{O}_3\text{S}$  : C, 53.27 ; H, 3.77 ; N, 6.54.

Found : C, 53.03 ; H, 3.70 ; N, 6.53.

#### Example 34

1-(4-Fluoro-3-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 93-94°C

IR (KBr) : 1500, 1400, 1310, 1275, 1225, 1160  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.28(3H, s), 3.21(3H, s), 3.39(2H, t,  $J=6.0\text{Hz}$ ), 3.76(2H, t,  $J=6.0\text{Hz}$ ), 6.85(1H, s), 6.96-7.91(7H, m).

MASS : 443( $M^++1$ ) Anal. Calcd for  $\text{C}_{20}\text{H}_{18}\text{F}_4\text{N}_2\text{O}_3\text{S}$  : C, 54.30; H, 4.10; N, 6.33.

Found : C, 53.62 ; H, 3.93 ; N, 6.28.

#### Example 35

1-(3-Methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 89-90°C

IR (KBr) : 1605, 1465, 1310, 1280, 1160, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.36(3H, s), 3.20(3H, s), 3.39 (2H, t,  $J=6.0\text{Hz}$ ), 3.75(2H, t,  $J=6.0\text{Hz}$ ), 6.85(1H, s), 6.95-7.90(8H, m).

MASS : 425( $M^++1$ )

Anal. Calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3\text{S} \cdot 1/3\text{H}_2\text{O}$  : C, 55.81 ; H, 4.61 ; N, 6.51.

Found : C, 55.89 ; H, 4.46 ; N, 6.63.

## Example 36

1-(3-Methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 92-93°C

IR (KBr) : 3475, 1510, 1465, 1310, 1280, 1240, 1160, 1115  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.37(3H, s), 2.60(1H, t,  $J=6.0\text{Hz}$ ), 3.34-3.39(2H, m), 3.99-4.07(2H, m), 6.86(1H, s), 6.93-7.92(8H, m).

MASS : 411( $M^+ + 1$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3\text{S}$  : C, 55.61 ; H, 4.17 ; N, 6.82.

Found : C, 55.32 ; H, 4.16 ; N, 6.69.

## Example 37

1-(3-Fluoro-4-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 136-137°C

IR (KBr) : 1595, 1505, 1460, 1400, 1310, 1280, 1245, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.30(3H, s), 3.21(3H, s), 3.40(2H, t,  $J=6.0\text{Hz}$ ), 3.77(2H, t,  $J=6.0\text{Hz}$ ), 6.84(1H, s), 6.90-7.92(7H, m).

MASS : 443( $M^+ + 1$ )

Anal. Calcd for  $\text{C}_{20}\text{H}_{18}\text{F}_4\text{N}_2\text{O}_3\text{S}$  : C, 54.30 ; H, 4.10 ; N, 6.33.

Found : C, 54.38 ; H, 4.03 ; N, 6.31.

## Example 38

1-(3-Fluoro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 100-101°C

IR (KBr) : 3480, 1595, 1470, 1415, 1310, 1280, 1245, 1160, 1120  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.31(3H, s), 2.60(2H, t,  $J=6.0\text{Hz}$ ), 3.38(2H, t,  $J=6.0\text{Hz}$ ), 4.04(2H, q,  $J=6.0\text{Hz}$ ), 6.85(1H, s), , 6.91-7.95(7H, m).

MASS : 429( $M^+ + 1$ )

Anal. Calcd for  $C_{19}H_{16}F_4N_2O_3S$  : C, 3.27 ; H, 3.77 ; N, 6.54.

Found : C, 53.32 ; H, 3.80 ; N, 6.44.

#### Example 39

5-{ 4-[(Acetoxymethyl)sulfinyl]-3-fluorophenyl}-1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of preparation 11 and Example 19.

IR (Neat) : 1750, 1500, 1270, 1220, 1150, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.10(3H, s), 3.94(3H, s), 5.41(2H, s), 6.76-7.51(7H, m).

MASS : 475( $M^+$ )

#### Example 40

1-(3-Chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-3-fluorophenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

IR (KBr) : 3435, 1615, 1505, 1270, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.43(1H, t,  $J=6.0\text{Hz}$ ), 3.52-4.25(4H, m), 3.95(3H, s), 6.83-7.937(7H, m).

MASS : 479( $M^++1$ )

#### Example 41

1-(4-Chloro-3-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 132-133°C

IR (KBr) : 1475, 1405, 1305, 1275, 1240, 1160, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.38(3H, s), 3.21(3H, s), 3.40(2H, t,  $J=6.0\text{Hz}$ ), 3.77(2H, t,  $J=6.0\text{Hz}$ ), 6.85(1H, s), 6.90-7.92(7H, m).

MASS : 459( $M^++1$ )

Anal. Calcd for  $C_{20}H_{18}ClF_3N_2O_3S$  : C, 52.35; H, 3.95; N, 6.10.

Found : C, 51.62 ; H, 3.84 ; N, 6.04.

#### Example 42

1-(4-Isopropenylphenyl)-5-[4-(acetoxymethylthio)phenyl]-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of



Preparation 11 and Example 19.

IR (Neat) : 1750, 1460, 1375, 1230, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.12(3H, s), 2.15(3H, s), 5.15(1H, m), 5.40(1H, m), 5.44(2H, s), 6.75(1H, s), 7.17-7.49(8H, m).

MASS : 455( $\text{M}^+$ +23)

Example 43

1-(4-Isopropenylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 141-143°C

IR (KBr) : 1510, 1305, 1280, 1240, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.15(3H, s), 3.21(3H, s), 3.40(2H, t,  $J=6.0\text{Hz}$ ), 3.76(2H, t,  $J=6.0\text{Hz}$ ), 5.17(1H, m), 5.41(1H, m), 6.85(1H, s), 7.22-7.91(8H, m).

MASS : 451( $\text{M}^+$ +1)

Example 44

1-(3-Methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 115-116°C

IR (KBr) : 3415, 1600, 1315, 1250, 1220, 1170, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.60(2H, t,  $J=6.0\text{Hz}$ ), 3.37(2H, t,  $J=6.0\text{Hz}$ ), 3.78(3H, s), 4.03(2H, q,  $J=6.0\text{Hz}$ ), 6.76-7.93(9H, m).

MASS : 427( $\text{M}^+$ +1)

Anal. Calcd for  $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_4\text{S}$  : C, 53.52 ; H, 4.02 ; N, 6.57.

Found : C, 53.32 ; H, 4.08 ; N, 6.54.

Example 45

1-(3-Chlorophenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 59-61°C

IR (KBr) : 1590, 1475, 1440, 1400, 1370, 1280, 1240, 1145  $\text{cm}^{-1}$

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 3.21(3H, s), 3.40(2H, t, J=6.0Hz), 3.76(2H, t, J=6.0Hz), 6.86(1H, s), 7.06-7.94(8H, m).

MASS : 445(M<sup>+</sup>+1)

Anal. Calcd for C<sub>19</sub>H<sub>16</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S : C, 51.30 ; H, 3.63 ; N, 6.30.

Found : C, 51.14 ; H, 3.49 ; N, 6.26.

#### Example 46

1-(4-Isopropylphenyl)-5-[4-(acetoxymethylthio)phenyl]-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Preparation 10 and Example 19.

IR (Neat) : 1750, 1510, 1465, 1375, 1230, 1135 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.25(6H, d, J=7.0Hz), 2.87-3.00(1H, m), 5.44(2H, s), 6.74(1H, s), 7.16-7.40(8H, m).

MASS : 457(M<sup>+</sup>+23)

#### Example 47

1-(4-Isopropylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 147-150°C

IR (KBr) : 1510, 1465, 1305, 1280, 1240, 1140 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.25(6H, d, J=7.0Hz), 2.84-2.98(1H, m), 3.20(3H, s), 3.39(2H, t, J=6.0Hz), 3.76(2H, t, J=6.0Hz), 6.84-7.90(9H, m).

MASS : 453(M<sup>+</sup>+1)

#### Example 48

5-[4-(Acetoxymethylsulfonyl)phenyl]-1-(3-cyano-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 19 and Example 20.

IR (KBr) : 2230, 1750, 1505, 1290, 1225, 1155, 1140 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.17(3H, s), 3.98(3H, s), 5.00(2H, ABq, J=10.0Hz), 6.84(1H, s), 6.96-7.73(7H, m).

#### Example 49

1-(3-Cyano-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-

phenyl)-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

mp : 142-143°C

IR (KBr) : 3510, 2230, 1505, 1285, 1235, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.57(1H, t,  $J=6.0\text{Hz}$ ), 3.99(3H, s), 4.03(2H, t,  $J=6.0\text{Hz}$ ), 6.87(1H, s), 6.98-7.98(7H, m).

MASS : 474( $\text{M}^+ + 23$ )

Anal. Calcd for  $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_4\text{S}$  : C, 53.21 ; H, 3.57; N, 9.31.

Found : C, 52.68 ; H, 3.56 ; N, 9.14.

#### Example 50

To a stirred suspension of NaH (about 60%, 12 mg) in N, N-dimethylformamide (0.3 ml) was added a solution of the 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole (147 mg) in N, N-dimethylformamide (0.4 ml) at an ice bath temperature. After 15 minutes methyl iodide (49mg) in N, N-dimethylformamide (0.3 ml) was added to this mixture at the same temperature. After 15 minutes, the reaction mixture was allowed to react at room temperature for 30 minutes. The mixture was diluted with water and then neutralized by addition of aqueous HCl dilute solution, and extracted with ethyl acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . The evaporation of solvent under reduced pressure gave a gummy oil, which was subjected to a column chromatography on silica gel eluting with a mixed solvent of ethyl acetate and n-hexane (2 : 1). Fractions containing the desired product were collected and concentrated under reduced pressure to give 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-methoxypropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (73 mg).

IR (Neat) : 1505, 1270, 1235, 1145  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.95-2.04(2H, m), 3.18-3.47(4H, m), 3.28(3H, s), 3.94(3H, s), 6.84-7.96(8H, m).

#### Example 51

A mixture of 1-(3-chloro-4-methoxyphenyl)-5-{4-[(ethoxycarbonyl)-

methylsulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (200 mg), hydroxyamine hydrochloric acid (30 mg) and sodium bicarbonate (55 mg) in ethanol (5 ml) was refluxed with stirring for 24 hours. The reaction mixture was concentrated under reduced pressure, and the resulting residue was diluted with water and extracted with ethyl acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . The evaporation of the solvent followed by column chromatography on silica gel eluting with ethyl acetate gave 1-(3-chloro-4-methoxyphenyl)-5-{4-[(N-hydroxycarbamoyl)methylsulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (48 mg).

IR (KBr) : 1740, 1505, 1318, 1275, 1230, 1160  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.91(3H, s), 4.07(2H, s), 6.86-8.21(8H, m).

MASS : 490(M+1)

#### Example 52

A mixture of 1-(3-chloro-4-methoxyphenyl)-5-{4-[(ethoxycarbonyl)methylsulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (250 mg) and 40% aqueous methylamine solution (0.5 ml) in ethanol (5 ml) was heated at reflux temperature for 8 hours. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (20 : 1) as an eluant, giving 1-(3-chloro-4-methoxyphenyl)-5-{4-[(methylcarbamoyl)methylsulfonyl]phenyl}-3-(trifluoromethyl)pyrazole (123 mg).

IR (KBr) : 3380, 1670, 1505, 1270, 1230, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.86(3H, d,  $J=5.0\text{Hz}$ ), 3.93(3H, s), 4.01(2H, s), 6.58(1H, br s), 6.85-7.90(8H, m).

MASS : 488(M+1)

#### Example 53

1-(3-Chloro-4-methoxyphenyl)-5-{4-[(2-oxopropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 7.

IR (KBr) : 1725, 1505, 1325, 1270, 1235, 1160  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.42(3H, s), 3.94(3H, s), 4.17(2H, s), 6.86-7.89(8H, m).

MASS : 473(M+1)

#### Example 54

5-{4-[(3-Acetoxypropyl)sulfonyl]phenyl}-1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3 and Example 12.

IR (KBr) : 1740, 1505, 1260, 1235, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.05-2.15(2H, m), 2.09(3H, s), 3.15-3.23(2H, m), 3.94(3H, s), 4.13(2H, t,  $J=6.0\text{Hz}$ ), 6.85-7.94(8H, m).

MASS : 539(M+23) API-ES

Anal. Calcd for  $\text{C}_{22}\text{H}_{20}\text{ClF}_3\text{N}_2\text{O}_5\text{S}$  : C, 51.12 ; H, 3.90 ; N, 5.42.

Found : C, 50.78 ; H, 3.87 ; N, 5.42.

#### Example 55

1-(3-Chloro-4-methoxyphenyl)-5-{4-[(3-(dimethylamino)propyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole hydrochloride was prepared by a similar procedure to that of Example 10.

mp : 213-215°C

IR (KBr) : 2615, 1505, 1280, 1240, 1160  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.95-2.06(2H, m), 2.70(6H, s), 3.07-3.18(2H, m), 3.46-3.54(2H, m), 4.01(3H, s), 7.20-7.97(8H, m)

MASS : 502( $M^+$ +1, free)

Anal. Calcd for  $\text{C}_{22}\text{H}_{23}\text{ClF}_3\text{N}_3\text{O}_3\text{S} \cdot \text{HCl}$  : C, 49.08; H, 4.49 ; N, 7.80.

Found : C, 48.83 ; H, 4.46 ; N, 7.69.

#### Example 56

1-(3-Chloro-4-methoxyphenyl)-5-{4-[(2-(dimethylamino)ethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole hydrochloride was prepared by a similar procedure to that of Example 10.

mp : 211-212°C

IR (KBr) : 2560, 2505, 2420, 1505, 1265, 1230, 1155  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 2.74(6H, s), 3.34-3.40(2H, m), 3.91(3H, s), 3.91-4.00(2H, m), 7.20-7.99(8H, m)

MASS : 488(M<sup>+</sup>+1, free)

Anal. Calcd for C<sub>21</sub>H<sub>21</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S · HCl : C, 48.10 ; H, 4.23 ; N, 8.01.

Found : C, 47.50 ; H, 4.20 ; N, 7.84.

#### Example 57

5-[4-(Acetoxymethylsulfonyl)phenyl]-1-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)pyrazole was prepared according to a similar manner to that of Preparation 10, Preparation 11, Example 19 and Example 20.

IR (KBr) : 1765, 1500, 1330, 1265, 1230, 1150 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 2.09(3H, s), 3.94(3H, s), 5.16(2H, s), 6.50-7.93(9H, m).

MASS : 471(M<sup>+</sup>+1)

#### Example 58

1-(3-Chloro-4-methoxyphenyl)-3-difluoromethyl-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole was prepared by a similar manner to that of Example 3.

mp : 120-122°C

IR (KBr) : 3465, 3440, 1505, 1455, 1410, 1300, 1290, 1265, 1145 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 1.63(1H, t, J=6.0Hz), 1.93-2.07(2H, m), 3.23-3.31(2H, m), 3.76(2H, q, J=6.0Hz), 3.94(3H, s), 6.52-7.92(9H, m).

MASS : 457(M<sup>+</sup>)

Anal. Calcd for C<sub>20</sub>H<sub>19</sub>ClF<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S : C, 52.58 ; H, 4.19 ; N, 6.13.

Found : C, 52.66 ; H, 4.26 ; N, 5.99.

#### Example 59

1-(3-Chloro-4-methoxyphenyl)-5-{4-[[2-(2-hydroxyethoxy)ethyl]-sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 7.

IR (Neat) : 3495, 1505, 1315, 1270, 1235, 1140 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 2.89-4.30(9H, m), 3.94(3H, s), 6.81-7.94(8H, m).

MASS : 505(M<sup>+</sup>+1)

#### Example 60

The key intermediate, 1-(4-bromo-3-methoxyphenyl)-5-(4-methylthiophenyl)-3-(trifluoromethyl)pyrazole, was prepared by refluxing a

mixture of 1, 1, 1-trifluoro-4-[4-(methylthio)phenyl]-2, 4-dioxobutane and 4-bromo-3-methoxyphenylhydrazine hydrochloride in acetic acid, which was converted to the desired product, 5-[4-(acetoxymethylthio)phenyl]-1-(4-bromo-3-methoxyphenyl)-3-(trifluoromethyl)pyrazole, according to a similar manner to that of Preparation 11 and Example 19.

IR (Neat) : 1750, 1595, 1475, 1410, 1255, 1220  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.12(3H, s), 3.81(3H, s), 5.45(2H, s), 6.67-7.52(8H, m).

MASS : 501( $\text{M}^+$ )

#### Example 61

1-(4-Bromo-3-methoxyphenyl)-3-trifluoromethyl-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole was prepared by a similar manner to that of Example 3.

mp : 123-124°C

IR (KBr) : 3505, 1595, 1405, 1280, 1225, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.55(1H, t,  $J=6.0\text{Hz}$ ), 3.39(2H, t,  $J=6.0\text{Hz}$ ), 3.84(3H, s), 4.07(2H, q,  $J=6.0\text{Hz}$ ), 6.59-7.97(8H, m).

MASS : 505( $\text{M}^+ + 2$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{16}\text{BrF}_3\text{N}_2\text{O}_4\text{S}$  : C, 45.16 ; H, 3.19 ; N, 5.54.

Found : C, 45.15 ; H, 3.18 ; N, 5.43.

#### Example 62

1-(4-Bromo-3-methoxyphenyl)-3-trifluoromethyl-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole was prepared by a similar manner to that of Example 3.

mp : 61-65°C

IR (KBr) : 3430, 1595, 1475, 1405, 1310, 1255, 1225, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.62(1H, t,  $J=6.0\text{Hz}$ ), 1.95-2.08(2H, s), 3.23-3.31(2H, m), 3.77(2H, q,  $J=6.0\text{Hz}$ ), 3.91(3H, s), 6.59-7.94(8H, m).

MASS : 519( $\text{M}^+$ )

Anal. Calcd for  $\text{C}_{20}\text{H}_{18}\text{BrF}_3\text{N}_2\text{O}_4\text{S}$  : C, 46.25 ; H, 3.49 ; N, 5.39.

Found : C, 46.85 ; H, 3.89 ; N, 5.05.

#### Example 63

The key intermediate, 1-(4-methoxyphenyl)-5-(4-methylthiophenyl)-3-difluoromethylpyrazole, was prepared by refluxing a mixture of 1, 1-difluoro-4-(4-methylthiophenyl)-2, 4-dioxobutane and 4-methoxyphenylhydrazine hydrochloride in acetic acid, which was converted to the desired product, 5-[4-(acetoxymethylsulfonyl)phenyl]-3-difluoromethyl-1-[4-(methoxyphenyl)pyrazole, according to a similar manner to that of Preparation 11, Example 19 and Example 20.

IR (KBr) : 1755, 1605, 1515, 1325, 1245, 1160  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.84(3H, s), 5.15(2H, s), 6.51-7.89(9H, m).

MASS : 437( $\text{M}^+ + 1$ )

#### Example 64

1-(4-Methoxyphenyl)-3-difluoromethyl-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole was prepared by a similar manner to that of Example 3.

mp : 80-81°C

IR (KBr) : 3470, 1515, 1305, 1240, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.64(1H, t,  $J=6.0\text{Hz}$ ), 3.37(2H, t,  $J=6.0\text{Hz}$ ), 3.84(3H, s), 4.03(2H, q,  $J=6.0\text{Hz}$ ), 6.51-7.90(9H, m).

MASS : 409( $\text{M}^+ + 1$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_4\text{S}$  : C, 55.88 ; H, 4.44 ; N, 6.86.

Found : C, 55.28; H, 4.37; N, 6.72.

#### Example 65

5-[4-(Acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-bromophenyl)pyrazole was prepared by a similar manner to that of Preparation 13, Example 19 and Example 20.

IR (KBr) : 1760, 1585, 1480, 1370, 1330, 1205  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.09(3H, s), 5.16(2H, s), 6.56(1H, s), 7.01-7.93(8H, m).

MASS : 469( $\text{M}^+$ )

#### Example 66

1-(3-Bromophenyl)-3-chloro-5-{4-(3-hydroxypropyl)sulfonyl}phenylpyrazole was prepared by a similar manner to that of Example 3.



IR (Neat) : 3435, 1585, 1480, 1370, 1310, 1145  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.63(1H, br s), 1.93-2.07(2H, m), 3.23-3.31(2H, m), 3.50-3.76(2H, m), 6.54(1H, s), 7.05-7.92(8H, m).

MASS : 519( $\text{M}^+ + 2$ )

#### Example 67

5-[4-(Acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-fluoro-4-methylphenyl)pyrazole was prepared by a similar procedure to that of Preparation 13, Example 21 and Example 22.

IR (KBr) : 1770, 1595, 1505, 1435, 1370, 1320, 1195  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.09(3H, s), 2.29(3H, s), 5.30(2H, s), 6.54(1H, s), 6.83-7.92(7H, m).

MASS : 423( $\text{M}^+ + 1$ )

#### Example 68

3-Chloro-1-(3-fluoro-4-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole was prepared by a similar manner to that of Example 3.

mp : 126-128°C

IR (KBr) : 1590, 1510, 1370, 1300, 1270, 1240, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.64(1H, t,  $J=6.0\text{Hz}$ ), 1.94-2.08(2H, m), 3.23-3.31(2H, m), 3.75(2H, q,  $J=6.0\text{Hz}$ ), 6.52(1H, s), 6.84-7.91(7H, m).

MASS : 409( $\text{M}^+ + 1$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{ClFN}_2\text{O}_3\text{S}$  : C, 55.81 ; H, 4.44 ; N, 6.85.

Found : C, 56.00 ; H, 4.48 ; N, 6.55.

#### Example 69

5-[(4-Acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-fluoro-3-methylphenyl)pyrazole was prepared by a similar manner to that of Preparation 13, Example 21 and Example 22.

IR (KBr) : 3135, 1765, 1595, 1500, 1375, 1335, 1240, 1200  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.07(3H, s), 2.26(3H, s), 5.15(2H, s), 6.55(1H, s), 6.90-7.90(7H, m).

MASS : 423( $\text{M}^+ + 1$ )

## Example 70

3-Chloro-1-(4-fluoro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}pyrazole was prepared by a similar manner to that of Example 3.

mp : 115-117°C

IR (KBr) : 3465, 1500, 1370, 1310, 1280, 1230, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.26(3H, s), 2.60(1H, t,  $J=6.0\text{Hz}$ ), 3.37(2H, t,  $J=6.0\text{Hz}$ ), 4.03(2H, t,  $J=6.0\text{Hz}$ ), 6.54(1H, s), 6.91-7.91(7H, m).

MASS : 395( $M^+ + 1$ )

Anal. Calcd for  $\text{C}_{18}\text{H}_{16}\text{ClFN}_2\text{O}_3\text{S}$  : C, 54.75 ; H, 4.09 ; N, 7.09.

Found : C, 54.51 ; H, 4.01 ; N, 6.98.

## Example 71

3-Chloro-1-(4-fluoro-3-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole was prepared by a similar manner to that of Example 3.

mp : 130-132°C

IR (KBr) : 3505, 3405, 1500, 1375, 1305, 1270, 1230, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.63(1H, t,  $J=6.0\text{Hz}$ ), 1.93-2.07(2H, m), 2.26(3H, s), 3.22-3.29(2H, m), 3.76(2H, q,  $J=6.0\text{Hz}$ ), 6.53(1H, s), 6.91-7.89(7H, m).

MASS : 409( $M^+ + 1$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{ClFN}_2\text{O}_3\text{S}$  : C, 55.81 ; H, 4.44 ; N, 6.85.

Found : C, 55.49 ; H, 4.39 ; N, 6.69.

## Example 72

3-Chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole was prepared by a similar manner to that of Example 3.

mp : 132-134°C

IR (KBr) : 3405, 1505, 1370, 1300, 1270, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.64(1H, t,  $J=5.0\text{Hz}$ ), 1.93-2.06(2H, m), 3.22-3.30(2H, m), 3.75(2H, q,  $J=6.0\text{Hz}$ ), 3.93(3H, s), 6.52(1H, s), 6.84-7.92(7H, m).

MASS : 441( $M^+$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$  : C, 51.71 ; H, 4.11 ; N, 6.35.

Found : C, 51.68 ; H, 4.17 ; N, 6.11.

Example 73

1-(3-Chlorophenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar procedure to that of Example 3.

IR (Neat) : 3460, 1590, 1475, 1280, 1235, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.38(2H, t,  $J=6.0\text{Hz}$ ), 3.78(1H, t,  $J=6.0\text{Hz}$ ), 4.01-4.19(2H, m), 6.84-7.96(9H, m).

MASS : 431( $\text{M}^+ + 1$ )

Example 74

3-Chloro-1-(4-isopropenylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole was prepared by a similar manner to that of Example 3.  
mp : 143-145°C

IR (KBr) : 3405, 1595, 1375, 1235, 1135  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 0.79-2.05(6H, m), 3.22-3.78(6H, m), 6.54(1H, s), 7.18-7.90(8H, m).

MASS : 417( $\text{M}^+ + 1$ )

Example 75

3-Chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 3.

mp : 153-154°C

IR (KBr) : 1600, 1505, 1300, 1270, 1150  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.21(3H, s), 3.39(2H, t,  $J=6.0\text{Hz}$ ), 3.75(2H, t,  $J=6.0\text{Hz}$ ), 3.92(3H, s), 6.49(1H, s), 6.83-7.90(7H, m)

MASS : 441( $\text{M}^+$ )

Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$  : C, 51.71 ; H, 4.11 ; N, 6.35.

Found : C, 51.14 ; H, 3.95 ; N, 6.22.

Example 76

5-[4-(4-Acetoxymethylthio)phenyl]-3-chloro-1-(4-chloro-3-methylphenyl)pyrazole was prepared by a similar procedure to that of

**Preparation 13 and Example 21.**

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.11(3H, s), 2.35(3H, s), 5.44(2H, s), 6.42(1H, s), 6.89(1H, dd, J=8.3 and 2.4Hz), 7.13-7.41(6H, m).

**Example 77**

3-Chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)-sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 3.

mp : 101-103°C

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.36(3H, s), 2.60(1H, t, J=6.4Hz), 3.37(2H, m), 4.02(2H, m), 6.54(1H, s), 6.87(1H, dd, J=8.6 and 2.4Hz), 7.27(2H, m), 7.43(2H, d, J=8.6Hz), 7.90(2H, d, J=8.6Hz).

MASS : 411(M<sup>+</sup>)

Anal. Calcd for C<sub>18</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S : C, 52.56 ; H, 3.92 ; N, 6.81.

Found : C, 52.52 ; H, 3.85 ; N, 6.75.

**Example 78**

3-Chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(3-hydroxypropyl)-sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 3.

mp : 113-115°C

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.62(1H, t, J=5.2Hz), 1.97(2H, m), 2.35(3H, s), 3.25(2H, m), 3.75(2H, m), 6.53(1H, s), 6.87(1H, dd, J=8.6 and 2.4Hz), 7.28(2H, m), 7.41(2H, d, J=8.4Hz), 7.89(2H, d, J=8.4Hz).

MASS : 425(M<sup>+</sup>)

**Example 79**

3-Chloro-1-(3-chloro-4-methylphenyl)-5-{4-[(3-hydroxypropyl)-sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 3.

mp : 105-106°C

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.67(1H, t, J=5.2Hz), 1.99(2H, m), 2.39(3H, s), 3.27(2H, m), 3.75(2H, q, J=5.7Hz), 6.53(1H, s), 6.94(1H, dd, J=8.0 and 2.2Hz), 7.18(1H, d, J=8.0Hz), 7.35(1H, d, J=2.2Hz), 7.41(2H, d, J=8.6Hz), 7.89(2H,

d, J=8.6Hz).

MASS : 425(M<sup>+</sup>)

Anal. Calcd for C<sub>19</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S : C, 53.65 ; H, 4.27 ; N, 6.59.

Found : C, 53.60 ; H, 4.21 ; N, 6.51.

#### Example 80

3-Chloro-1-(3-chloro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)-sulfonyl]phenyl}pyrazole was prepared by a similar procedure to that of Example 3.

mp : 108-110°C

NMR (CDCl<sub>3</sub>, δ) : 2.39(3H, s), 2.62(1H, t, J=6.4Hz), 3.37(2H, m), 4.04(2H, m), 6.53(1H, s), 6.94(1H, dd, J=8.0 and 2.2Hz), 7.23(1H, d, J=8.0Hz), 7.34(1H, d, J=2.2Hz), 7.42(2H, d, J=8.6Hz), 7.90(2H, d, J=8.6Hz).

MASS : 413(M<sup>+</sup>+2)

Anal. Calcd for C<sub>18</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S : C, 52.56; H, 3.92; N, 6.81.

Found : C, 51.92 ; H, 3.85 ; N, 6.62.

#### Example 81

3-Chloro-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-1-(4-methylphenyl)pyrazole was obtained from 4-[3-chloro-1-(4-methylphenyl)pyrazol-5-yl]benzenesulfinate in the similar manner that of Example 3.

NMR (DMSO-d<sub>6</sub>, δ) : 1.60-1.75(2H, m), 2.34(3H, s), 3.28-3.45(4H, m), 4.64(1H, t, J=5.3Hz), 6.96(1H, s), 7.18(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.51(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz).

IR (KBr) : 3512, 3400, 3128, 2964, 2924, 2881, 1601 cm<sup>-1</sup>.

Mass m/e : 391 (M<sup>+</sup>+1).

#### Example 82

5-[4-(Acetoxymethylthio)phenyl]-3-chloro-1-(3-methylphenyl)pyrazole was obtained from 3-chloro-1-(3-methylphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole in a similar manner that of Example 21.

NMR (DMSO-d<sub>6</sub>, δ) : 2.04(3H, s), 2.31(3H, s), 5.53(2H, s), 6.82(1H, s), 6.97-7.01(1H, m), 7.20-7.34(5H, m), 7.42(2H, d, J=8.4Hz).

IR (KBr) : 3654, 3118, 3047, 2958, 2924, 2868, 1738, 1603  $\text{cm}^{-1}$ .

Mass  $m/e$  : 373 ( $M^+ + 1$ ).

#### Example 83

5-[4-(Acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-methylphenyl)-pyrazole was obtained from 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(3-methylphenyl)pyrazole in the similar manner that of Example 22.

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 2.03(3H, s), 2.31(3H, s), 5.44(2H, s), 6.98-7.02(1H, m), 7.00(1H, s), 7.21-7.34(3H, m), 7.54(2H, d,  $J=8.4\text{Hz}$ ), 7.90(2H, d,  $J=8.4\text{Hz}$ ).

IR (KBr) : 3516, 3134, 3082, 3008, 2945, 1765  $\text{cm}^{-1}$ .

Mass  $m/e$  : 405 ( $M^+ + 1$ ).

#### Example 84

3-Chloro-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-1-(3-methylphenyl)-pyrazole was obtained from sodium 4-[3-chloro-1-(3-methylphenyl)-pyrazol-5-yl]benzenesulfinate in the similar manner that of Example 3.

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 2.30(3H, s), 3.48(2H, t,  $J=6.1\text{Hz}$ ), 3.62-3.71(2H, m), 4.88(1H, t,  $J=5.3\text{Hz}$ ), 6.97(1H, s), 6.95-7.03(1H, m), 7.20-7.34(3H, m), 7.49(2H, d,  $J=8.4\text{Hz}$ ), 7.88(2H, d,  $J=8.4\text{Hz}$ ).

IR (KBr) : 3464, 3406, 3132, 3055, 3960, 2916, 1601  $\text{cm}^{-1}$ .

Mass  $m/e$  : 377 ( $M^+ + 1$ ).

#### Example 85

5-[4-(Acetoxymethylthio)phenyl]-3-chloro-1-phenylpyrazole was prepared by a similar method to that of Example 21.  
yellow oil.

IR (Neat) : 1751, 1738, 1598, 1490  $\text{cm}^{-1}$ .

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 2.06(3H, s), 5.53(2H, s), 6.83(1H, s), 7.20-7.50(9H, m).

MS ( $m/z$ ) : 359( $M^+ + 1$ ).

#### Example 86

5-[4-(Acetoxymethylsulfonyl)phenyl]-3-chloro-1-phenylpyrazole was prepared by a similar method to that of Example 22.  
white crystals.

mp : 139-142°C.

IR (KBr) : 1758, 1594, 1492, 1434  $\text{cm}^{-1}$ .

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.03(3H, s), 5.43 (2H, s), 7.01(1H, s), 7.20-7.50(5H, m)  
7.53(2H, dd, J=7, 2Hz), 7.89(2H, dd, J=7, 2Hz) ,

MS(m/z) : 391( $M^{+1}$ ).

#### Example 87

3-Chloro-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-1-phenylpyrazole was prepared by the two step procedure. In step one, the starting material was hydrolized by a similar method to that of Preparation 14, and followed by alkylation by a similar method to that of Example 3.

white crystals.

mp : 110-112°C

IR (KBr) : 3500, 3490, 3400, 1596, 1492  $\text{cm}^{-1}$ .

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.50-1.80(2H, m), 3.30-3.50(4H, m), 4.65(1H, t, J=5Hz),  
6.99(1H, s), 7.25-7.60(7H, m), 7.87(2H, d, J=8Hz)

MS(m/z) : 377( $M^{+1}$ ).

Anal. Calcd. for  $C_{18}H_{17}ClN_2O_3S$  : C, 57.37 ; H, 4.55 ; N, 7.43.

Found (1/6 $H_2O$ ) : C, 56.92 ; H, 4.60 ; N, 7.37.

#### Example 88

5-[4-(Acetoxymethylthio)phenyl]-3-chloro-1-(4-chloro-3-methoxyphenyl)pyrazole was prepared by a similar method to that of Example 21.  
white crystals.

mp : 120-124°C

IR (KBr) : 1737, 1594, 1488  $\text{cm}^{-1}$ .

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.04(3H, s), 3.75(3H, s), 5.53(2H, s), 6.79(1H, dd, J=8,  
2Hz), 6.85(1H, s), 7.15(1H, s), 7.10-7.50(5H, m).

MS(m/z) : 423( $M^{+1}$ ), 425( $M^{+3}$ ).

#### Example 89

5-[4-(Acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-chloro-3-methoxyphenyl)pyrazole was prepared by a similar method to that of Example 22.  
white crystals.

mp : 124-125°C

IR (KBr) : 1766, 1594, 1490, 1459  $\text{cm}^{-1}$ .

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 2.04(3H, s), 3.75(3H, s), 5.44(2H, s), 6.79(1H, dd,  $J=8$ , 2Hz), 7.03(1H, s), 7.15(1H, d,  $J=2$ Hz), 7.46(1H, d,  $J=8$ Hz), 7.57(2H, d,  $J=8$ Hz), 7.92(2H, d,  $J=8$ Hz).

MS( $m/z$ ) : 455( $M^{+1}$ ), 457( $M^{+3}$ )

#### Example 90

3-Chloro-1-(4-chloro-3-methoxyphenyl)-5-{4-[(3-hydroxypropyl)-sulfonyl]phenyl}pyrazole was prepared by the two step procedure. In step one, the starting material was hydrolized by similar method as that described for Preparation 14, and followed by alkylation by similar method to that described for Example 3.

white crystals.

mp ; 113-114°C

IR (KBr) : 3519, 3465, 3403, 1594, 1488  $\text{cm}^{-1}$ .

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.50-1.80(2H, m), 3.30-3.50(4H, m), 3.73(3H, s), 4.65(1H, t,  $J=5$ Hz), 6.79(1H, dd,  $J=8$ , 2Hz), 7.01(1H, s), 7.15(1H, d,  $J=2$ Hz), 7.47(1H, d,  $J=8$ Hz), 7.56(2H, d,  $J=8$ Hz), 7.91(2H, d,  $J=8$ Hz).

MS( $m/z$ ) : 441( $M^{+1}$ ), 443( $M^{+3}$ ).

Anal. Calcd for  $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_3\text{S}$  : C, 51.71 ; H, 4.11 ; N, 6.35.

Found : C, 51.57 ; H, 4.06 ; N, 6.26.

#### Example 91

5-[4-(Acetoxymethylthio)phenyl]-3-chloro-1-(3-chlorophenyl)-pyrazole was prepared by a similar procedure to that of Example 21.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.11(3H, s), 5.44(2H, s), 6.44(1H, s), 7.06 (1H, pd, t,  $J=8$ Hz), 7.17(2H, d,  $J=8$ Hz), 7.19-7.43(3H, m), 7.40(2H, d,  $J=8$ Hz).

IR (Neat) : 1747  $\text{cm}^{-1}$

mass ( $m/z$ ) : 393( $M+1$ )

#### Example 92

5-[4-(Acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-chlorophenyl)-pyrazole was prepared by a similar procedure to that of Example 22.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.10(3H, s), 5.16(2H, s), 6.56(1H, s), 7.01(1H, dt,  $J=8.1$ Hz),



7.26-7.47(3H, m), 7.44(2H, d, J=8Hz), 7.91(2H, d, J=8Hz).

IR (KBr) : 1766, 1328, 1151  $\text{cm}^{-1}$

mass (m/z) : 425(M+1)

#### Example 93

3-Chloro-1-(3-chlorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-pyrazole was prepared a similar procedure to that of Example 3.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.72(1H, t, J=5Hz), 1.92-2.07(2H, m), 3.22-3.31(2H, m), 3.75(2H, q, J=6Hz), 6.55(1H, s), 7.04(1H, dt, J=8.2Hz), 7.23-7.45(1H, m), 7.42(2H, d, J=9Hz), 7.90(2H, d, J=9Hz).

IR (KBr) : 3405, 1305  $\text{cm}^{-1}$

mass (m/z) : 411(M+1)

mp : 108-110°C

#### Example 94

5-[4-(Acetoxymethylthio)phenyl]-3-chloro-1-(4-chlorophenyl)pyrazole was prepared by a similar procedure to that of Example 21.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.11(3H, s), 5.44(2H, s), 6.43(1H, s), 7.15(2H, d, J=9Hz), 7.21(2H, d, J=9Hz), 7.32(1H, d, J=9Hz), 7.39(2H, d, J=9Hz).

IR (Neat) : 1745  $\text{cm}^{-1}$

mass (m/z) : 393(M+1)

#### Example 95

5-[4-(Acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-chlorophenyl)-pyrazole was prepared by a similar procedure to that of Example 22.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.08(3H, s), 5.16(2H, s), 6.56(1H, s), 7.18(2H, d, J=9Hz), 7.35(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.90(2H, d, J=9Hz).

IR (KBr) : 1758, 1330, 1149  $\text{cm}^{-1}$

mass (m/z) : 425(M+1)

#### Example 96

3-Chloro-1-(4-chlorophenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-pyrazole was prepared by a similar procedure to that of Example 3.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.61(1H, t, J=6Hz), 3.35-3.40(2H, m), 4.00-4.09(2H, m), 6.54(1H, s), 7.19(2H, d, J=9Hz), 7.35(2H, d, J=9Hz), 7.42(2H, d, J=9Hz),

7.91(2H, d, J=9Hz), 7.35(2H, d, J=8.9Hz), 7.42(2H, d, J=8.6Hz), 7.91(2H, d, J=8.6Hz).

IR (KBr) : 3469, 1309  $\text{cm}^{-1}$

mass (m/z) : 397(M+1)

mp : 150-151°C

#### Example 97

3-Chloro-1-(4-chlorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-pyrazole was prepared by a similar procedure to that of Example 3

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.67(1H, t, J=5Hz), 1.94-2.08(2H, m), 3.22-3.31(2H, m), 3.77(2H, q, J=6Hz), 6.54(1H, s), 7.19(2H, d, J=9Hz), 7.35(2H, d, J=9Hz), 7.41(2H, d, J=9Hz), 7.89(2H, d, J=9Hz).

IR (KBr) : 3403, 1305  $\text{cm}^{-1}$

mass (m/z) : 411(M+1)

mp : 156-158°C

#### Example 98

5-[4-(Acetoxymethylthio)phenyl]-3-chloro-1-(4-fluorophenyl)pyrazole was prepared by a similar procedure to that of Example 21.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.11(3H, s), 5.43(2H, s), 6.43(1H, s), 7.04(2H, t, J=9Hz), 7.14(2H, d, J=9Hz), 7.22-7.29(2H, m), 7.38(2H, d, J=9Hz).

IR (Neat) : 1747  $\text{cm}^{-1}$

mass (m/z) : 377(M+1)

#### Example 99

5-[4-(Acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-fluorophenyl)-pyrazole was prepared by a similar procedure to that of Example 22.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.08(3H, s), 5.15(2H, s), 6.56(1H, s), 7.08(2H, t, J=9Hz), 7.19-7.27(2H, m), 7.41(2H, d, J=9Hz), 7.89(2H, d, J=9Hz).

IR (KBr) : 1770, 1317, 1157  $\text{cm}^{-1}$

mass (m/z) : 409(M+1)

#### Example 100

3-Chloro-1-(4-fluorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-pyrazole was prepared by a similar procedure to that of Example 3.

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.63(1H, t, J=5Hz), 1.94-2.08(2H, m), 3.26(2H, t, J=8Hz), 2.77(q, J=5Hz), 6.54(1H, s), 7.07(2H, t, J=9Hz), 7.20-7.28(2H, m), 7.40(2H, d, J=8Hz), 7.88(2H, d, J=8Hz).

IR (KBr) : 3403, 1305 cm<sup>-1</sup>

mass (m/z) : 395(M+1)

mp : 125-126°C

#### Example 101

5-(4-Methylphenyl)-1-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar manner to that of Example 3.

IR (Neat) : 1595, 1465, 1320, 1270, 1240, 1140 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.38(3H, s), 3.22(3H, s), 3.39(2H, t, J=6.0Hz), 3.77(2H, t, J=6.0Hz), 6.75(1H, s), 7.08-7.92(9H, m).

MASS : 425(M<sup>+</sup>+1)

#### Example 102

5-(4-Methylphenyl)-1-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar manner to that of Example 3.

IR (Neat) : 3475, 1465, 1275, 1235, 1135 cm<sup>-1</sup>

#### Example 103

5-(4-Chloro-3-methoxyphenyl)-1-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole was prepared by a similar manner to that of Example 3.

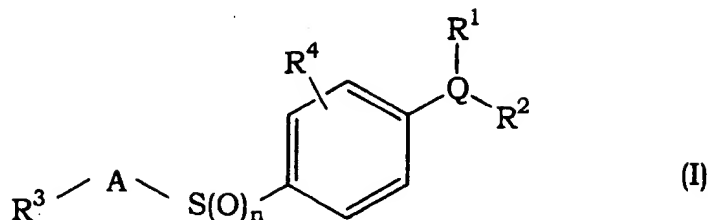
IR (Neat) : 3480, 1665, 1475, 1315, 1280, 1240, 1140 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.38(3H, s), 2.59 (1H, t, J=6.0Hz), 3.38(2H, t, J=6.0Hz), 4.04(2H, q, J=6.0Hz), 6.86(1H, s), 6.90-8.02(7H, m).

MASS : 445(M<sup>+</sup>+1)

## CLAIMS

1. A compound of the formula (I):



wherein

$R^1$  is halo(lower)alkyl, halogen or cyano,

$R^2$  is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, lower alkoxy, cyano, nitro, lower alkenyl, amino, acyl and hydroxyimino,

$R^3$  is hydrogen, hydroxy, acyloxy, lower alkoxy optionally substituted with lower alkoxy, amino optionally substituted with hydroxy or lower alkyl, lower alkylthio, or lower alkylsulfonyl,

$R^4$  is hydrogen or halogen,

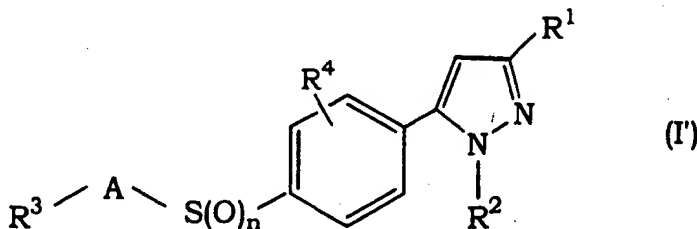
Q is pyrazolyl,

A is lower alkylene optionally substituted with oxo or hydroxy, and

n is 0, 1 or 2,

provided that when  $R^3$  is hydrogen,  $R^2$  is aryl substituted with lower alkenyl or A is lower alkylene substituted with oxo, or its salt.

2. A compound of the formula (I')



wherein

R<sup>1</sup> is halo(lower)alkyl, halogen or cyano,  
R<sup>2</sup> is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, lower alkoxy, cyano, nitro, lower alkenyl, amino, acyl and hydroxyimino,  
R<sup>3</sup> is hydroxy, acyloxy, lower alkoxy optionally substituted with lower alkoxy, amino optionally substituted with hydroxy or lower alkyl, lower alkylthio, or lower alkylsulfonyl,  
R<sup>4</sup> is hydrogen or halogen,  
A is lower alkylene optionally substituted with oxo or hydroxy, and  
n is 0, 1 or 2,  
provided that when R<sup>3</sup> is hydrogen, R<sup>2</sup> is aryl substituted with lower alkenyl or A is lower alkylene substituted with oxo, or its salt.

3. The compound according to claim 2, wherein

R<sup>1</sup> is trifluoromethyl, difluoromethyl, chlorine or cyano,  
R<sup>2</sup> is phenyl, tolyl, or phenyl or tolyl substituted with substituent(s) selected from the group consisting of chlorine, fluorine, bromine and methoxy,  
R<sup>3</sup> is hydroxy, acetoxy, ethoxy, amino, methylamino, methylthio or methylsulfonyl,  
R<sup>4</sup> is hydrogen,  
A is dimethylene, trimethylene, methylene or pentamethylene, and  
n is 2.

4. The compound according to claim 3, which is a compound selected from the group consisting of

- (1) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-chloro-4-methoxyphenyl)pyrazole,
- (2) 5-[4-(acetoxymethylsulfonyl)phenyl]-1-(3-chloro-4-methoxy-phenyl)-3-(trifluoromethyl)pyrazole,
- (3) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]-

- phenyl)-3-(trifluoromethyl)pyrazole,
- (4) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (5) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (6) 1-(3-chloro-4-methoxyphenyl)-5-{4-[[2-(methylthio)ethyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (7) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(5-hydroxypentyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (8) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(4-hydroxybutyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (9) 1-(3-chloro-4-methoxyphenyl)-5-[4-(ethoxycarbonylmethylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole,
- (10) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-methylaminoethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (11) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-aminoethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (12) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-acetoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (13) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-acetoxyethyl)sulfonyl]phenyl}pyrazole,
- (14) 1-(3-chloro-4-methoxyphenyl)-5-{4-[[2-(methylsulfonyl)ethyl]sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (15) 5-{4-[(acetoxymethyl)sulfonyl]phenyl}-1-(4-fluorophenyl)-3-(trifluoromethyl)pyrazole,
- (16) 1-(4-fluorophenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (17) 5-{4-[(acetoxymethyl)sulfonyl]phenyl}-1-(4-chloro-3-methoxyphenyl)-3-cyanopyrazole,
- (18) 1-(4-chloro-3-methoxyphenyl)-5-{4-[2-hydroxyethyl]sulfonyl]phenyl}-3-cyanopyrazole,

- (19) 5-[4-(acetoxymethylthio)phenyl]-1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazole,
- (20) 5-[4-(acetoxymethylsulfonyl)phenyl]-1-(3-chlorophenyl)-3-(trifluoromethyl)pyrazole,
- (21) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-methylphenyl)-pyrazole,
- (22) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-methylphenyl)-pyrazole,
- (23) 3-chloro-1-(4-isopropenyl-phenyl)-5-[4-(methylsulfinyl)-phenyl]pyrazole,
- (24) 5-[(4-acetoxymethylthio)phenyl]-3-chloro-1-(isopropenylphenyl)-pyrazole,
- (25) 3-chloro-1-(4-isopropenylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]-phenyl}pyrazole,
- (26) 3-chloro-1-(4-isopropenylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}pyrazole,
- (27) 1-(4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (28) 1-(4-methylphenyl)-5-{4-[(3-acetoxypentyl)sulfonyl] phenyl}-3-(trifluoromethyl)pyrazole,
- (29) 1-(4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (30) 5-[4-(acetoxymethylthio)phenyl]-3-trifluoromethyl-1-[(3-chloro-4-methyl)phenyl]pyrazole,
- (31) 1-(3-chloro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (32) 1-(3-chloro-4-methylphenyl)-5-{4-[(2-acetoxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (33) 1-(4-fluoro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (34) 1-(4-fluoro-3-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]-

- phenyl}-3-(trifluoromethyl)pyrazole,
- (35) 1-(3-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (36) 1-(3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (37) 1-(3-fluoro-4-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (38) 1-(3-fluoro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (39) 5-{4-[(acetoxymethyl)sulfinyl]-3-fluorophenyl}-1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole,
- (40) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]-3-fluorophenyl}-3-(trifluoromethyl)pyrazole,
- (41) 1-(4-chloro-3-methylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (42) 1-(1-hydroxy-1-methylethyl)-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole,
- (43) 1-(4-isopropenylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (44) 1-(3-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (45) 1-(3-chlorophenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (46) 1-(4-isopropylphenyl)-5-[4-(acetoxymethylthio)phenyl]-3-(trifluoromethyl)pyrazole,
- (47) 1-(4-isopropylphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (48) 5-[4-(acetoxymethylsulfonyl)phenyl]-1-(3-cyano-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole,
- (49) 1-(3-cyano-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,



- (50) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-methoxypropyl)sulfonyl]-phenyl}-3-(trifluoromethyl)pyrazole,
- (51) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(N-hydroxycarbamoyl)-methylsulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (52) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(methylcarbamoyl)methylsulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (53) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-oxopropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (54) 5-{4-[(3-acetoxypentyl)sulfonyl]phenyl}-1-(3-chloro-4-methoxyphenyl)-3-(trifluoromethyl)pyrazole,
- (55) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-(dimethylamino)propyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole hydrochloride,
- (56) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-(dimethylamino)ethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole hydrochloride,
- (57) 5-[4-(acetoxymethylsulfonyl)phenyl]-1-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)pyrazole,
- (58) 1-(3-chloro-4-methoxyphenyl)-3-difluoromethyl-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (59) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-(2-hydroxyethoxy)ethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,
- (60) 5-[4-(acetoxymethylthio)phenyl]-1-(4-bromo-3-methoxyphenyl)-3-(trifluoromethyl)pyrazole,
- (61) 1-(4-bromo-3-methoxyphenyl)-3-trifluoromethyl-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (62) 1-(4-bromo-3-methoxyphenyl)-3-trifluoromethyl-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (63) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-difluoromethyl-1-[4-(methoxyphenyl)pyrazole,
- (64) 1-(4-methoxyphenyl)-3-difluoromethyl-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (65) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-bromophenyl)-

pyrazole,

(66) 1-(3-bromophenyl)-3-chloro-5-{4-(3-hydroxypropyl)sulfonyl}-phenyl}pyrazole,

(67) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-fluoro-4-methylphenyl)pyrazole,

(68) 3-chloro-1-(3-fluoro-4-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

(69) 5-[(4-acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-fluoro-3-methylphenyl)pyrazole,

(70) 3-chloro-1-(4-fluoro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,

(71) 3-chloro-1-(4-fluoro-3-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

(72) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

(73) 1-(3-chlorophenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

(74) 3-chloro-1-(4-isopropenylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

(75) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-methoxyethyl)sulfonyl]phenyl}pyrazole hydrochloride,

(76) 5-[4-(4-acetoxymethylthio)phenyl]-3-chloro-1-(4-chloro-3-methylphenyl)pyrazole,

(77) 3-chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,

(78) 3-chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

(79) 3-chloro-1-(3-chloro-4-methylphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

(80) 3-chloro-1-(3-chloro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,

- (81) 3-chloro-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-1-(4-methylphenyl)pyrazole,
- (82) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(3-methylphenyl)pyrazole,
- (83) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-methylphenyl)-pyrazole,
- (84) 3-chloro-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-1-(3-methylphenyl)pyrazole,
- (85) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-phenylpyrazole,
- (86) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-phenylpyrazole,
- (87) 3-chloro-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-1-phenylpyrazole,
- (88) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-chloro-3-methoxyphenyl)pyrazole,
- (89) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-chloro-3-methoxyphenyl)pyrazole,
- (90) 3-chloro-1-(4-chloro-3-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (91) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(3-chlorophenyl)pyrazole,
- (92) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(3-chlorophenyl)pyrazole,
- (93) 3-chloro-1-(3-chlorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,
- (94) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-chlorophenyl)pyrazole,
- (95) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-chlorophenyl)pyrazole,
- (96) 3-chloro-1-(4-chlorophenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,
- (97) 3-chloro-1-(4-chlorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]-

phenyl}pyrazole,

(98) 5-[4-(acetoxymethylthio)phenyl]-3-chloro-1-(4-fluorophenyl)-pyrazole,

(99) 5-[4-(acetoxymethylsulfonyl)phenyl]-3-chloro-1-(4-fluorophenyl)-pyrazole,

(100) 3-chloro-1-(4-fluorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}pyrazole,

(101) 5-(4-methylphenyl)-1-{4-[(2-methoxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

(102) 5-(4-methylphenyl)-1-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole, and

(103) 5-(4-chloro-3-methoxyphenyl)-1-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole.

5. The compound according to claim 4, which is a compound selected from the group consisting of

(1) 1-(3-chloro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

(2) 1-(3-fluoro-4-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

(3) 1-(4-fluoro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

(4) 1-(4-bromo-3-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

(5) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

(6) 1-(3-chloro-4-methoxyphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole,

(7) 3-chloro-1-(4-isopropenylphenyl)-5-{4-[(2-hydroxyethyl)sulfonyl]phenyl}pyrazole,

(8) 3-chloro-1-(4-chlorophenyl)-5-{4-[(3-hydroxypropyl)sulfonyl]-

phenyl}pyrazole,

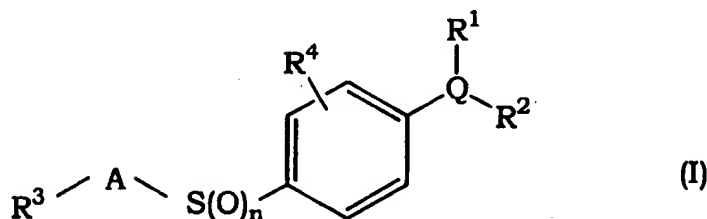
(9) 3-chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(2-hydroxyethyl)-sulfonyl]phenyl}pyrazole,

(10) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-{4-[(3-hydroxypropyl)-sulfonyl]phenyl}pyrazole,

(11) 3-chloro-1-(4-chloro-3-methylphenyl)-5-{4-[(3-hydroxypropyl)-sulfonyl]phenyl}pyrazole, and

(12) 5-(4-chloro-3-methoxyphenyl)-1-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-3-(trifluoromethyl)pyrazole.

6. A process for preparing a compound of the formula (I):



wherein

$R^1$  is halo(lower)alkyl, halogen or cyano,

$R^2$  is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, lower alkoxy, cyano, nitro, lower alkenyl, amino, acyl and hydroxyimino,

$R^3$  is hydrogen, hydroxy, acyloxy, lower alkoxy optionally substituted with lower alkoxy, amino optionally substituted with hydroxy or lower alkyl, lower alkylthio, or lower alkylsulfonyl,

$R^4$  is hydrogen or halogen,

Q is pyrazolyl,

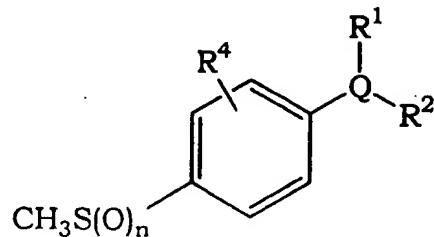
A is lower alkylene optionally substituted with oxo or hydroxy, and

n is 0, 1 or 2,

provided that when  $R^3$  is hydrogen,  $R^2$  is aryl substituted with lower

alkenyl or A is lower alkylene substituted with oxo, or its salt,  
which comprises,

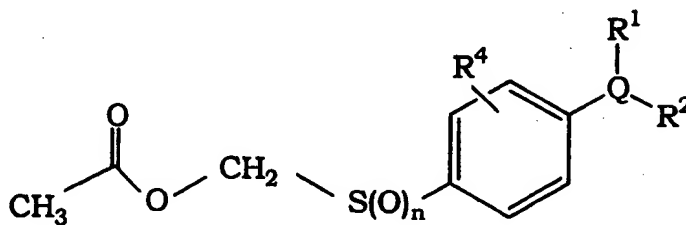
(1) reacting a compound of the formula (II)



(II)

or its salt

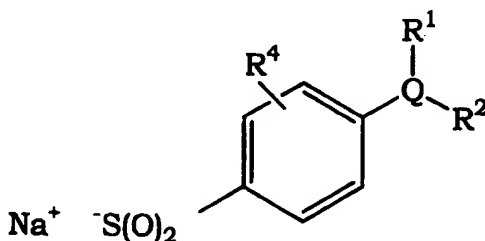
wherein  $R^1$ ,  $R^2$ ,  $R^4$ , Q and n are as defined above,  
with  $\text{CH}_3\text{COONa}$  or  $(\text{CH}_3\text{CO})_2\text{O}$   
to give a compound of the formula (I-1)



(I-1)

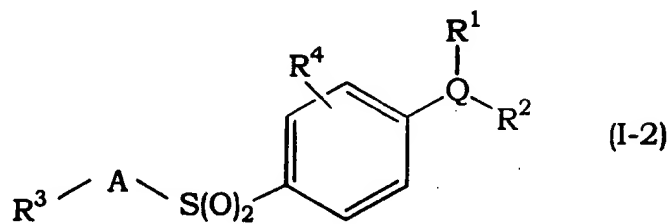
or its salt

wherein  $R^1$ ,  $R^2$ ,  $R^4$ , Q and n are as defined above,  
(2) reacting a compound of the formula (IV):



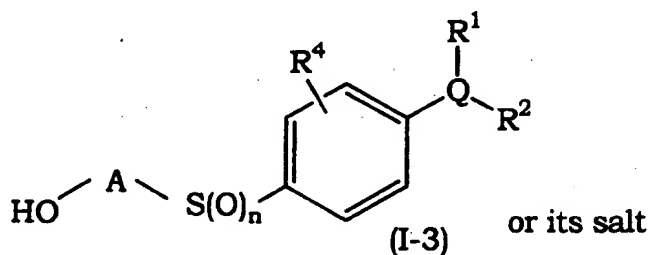
(IV)

wherein  $R^1$ ,  $R^2$ ,  $R^4$  and Q are as defined above,  
 with a compound (V):  $R^3$ -A-Hal wherein A and  $R^3$  are as defined above, or  
 its salt,  
 to give a compound (I-2):



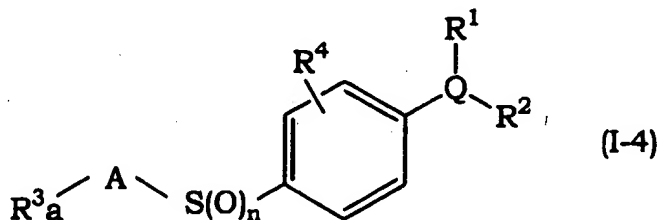
or its salt

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , A and Q are as defined above,  
 (3) subjecting a compound of the formula (I-3):



or its salt

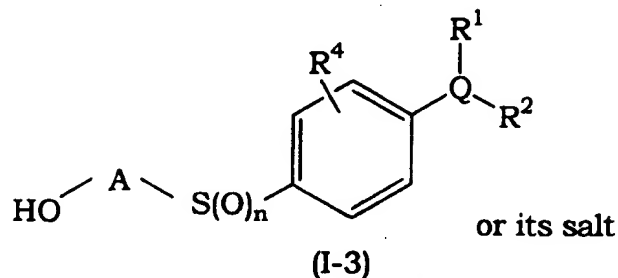
wherein  $R^1$ ,  $R^2$ ,  $R^4$ , A, Q and n are as defined above,  
 to amination to give a compound of the formula (I-4)



or its salt

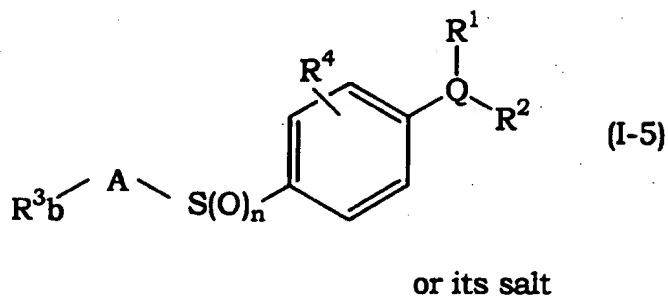
wherein  $R^{3a}$  is amino optionally substituted with hydroxy or lower alkyl, and  $R^1$ ,  $R^2$ ,  $R^4$ , A, Q and n are as defined above,

(4) subjecting a compound of the formula (I-3)



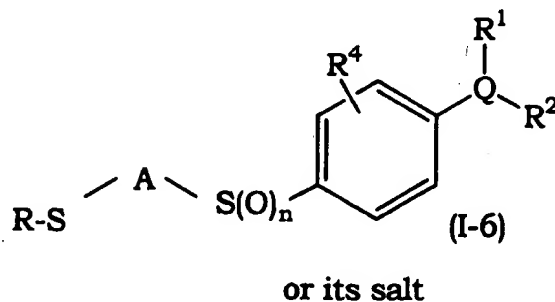
wherein  $R^1$ ,  $R^2$ ,  $R^4$ , A, Q and n are as defined above,

to acylation to give a compound of the formula (I-5)



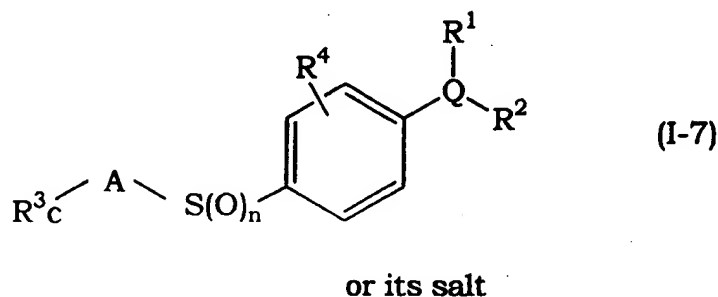
wherein  $R^{3b}$  is acyl, and  $R^1$ ,  $R^2$ ,  $R^4$ , A, Q and n are as defined above, or

(5) subjecting a compound of the formula (I-6)





wherein R is lower alkyl, and R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, A, Q and n are as defined above, to oxydation to give a compound of the formula (I-7)



wherein R<sup>3</sup>c is lower alkylsulfonyl, and R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, A, Q and n are as defined above.

7. A pharmaceutical composition comprising the compound of claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.

8. A compound of claim 1 for use as a medicament.

9. A COX-II inhibiting agent comprising the compound of claim 1.

10. A method for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegenerative diseases which comprises administering an effective amount of the compound of claim 1 to human beings or animals.

11. Use of the compound of claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegenerative diseases

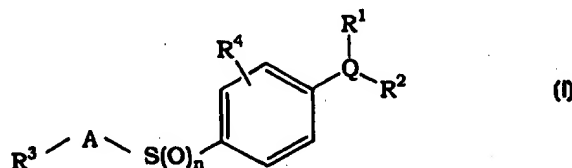
in human beings or animals.

12. Use of the compound of claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegenerative diseases in human beings or animals.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/JP99/05289  <b>(22) International Filing Date:</b> 27 September 1999 (27.09.99)  <b>(30) Priority Data:</b> PP 6231 30 September 1998 (30.09.98) AU PQ 2243 16 August 1999 (16.08.99) AU  <b>(71) Applicant (for all designated States except US):</b> FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KONISHI, Nobukiyo [JP/JP]; 22-7, Aotanai, Nagaokakyo-shi, Kyoto 617-0811 (JP). NAKAMURA, Katsuya [JP/JP]; 12-1-103, Kamihamuro 2-chome, Takatsuki-shi, Osaka 569-1044 (JP). YAMAMOTO, Hirofumi [JP/JP]; 1-4-22-207, Kashio, Takarazuka-shi, Hyogo 665-0054 (JP). MANABE, Takashi [JP/JP]; 1-2-103, Maruyamadai, Kawanishi-shi, Hyogo 666-0152 (JP).  <b>(74) Agent:</b> TAKASHIMA, Hajime; Yuki Building, 3-9, Hiranomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-0046 (JP).		<b>(81) Designated States:</b> BR, CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> 8 June 2000 (08.06.00)

**(54) Title:** PYRAZOLE COMPOUNDS AS COX-2 INHIBITORS**(57) Abstract**

A compound of formula (I), wherein R<sup>1</sup> is halo(lower)alkyl, halogen or cyano, R<sup>2</sup> is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, lower alkoxy, cyano, nitro, lower alkenyl, amino, acyl and hydroxyimino, R<sup>3</sup> is hydrogen, hydroxy, acyloxy, lower alkoxy optionally substituted with lower alkoxy, amino optionally substituted with hydroxy or lower alkyl, lower alkylthio, or lower alkylsulfonyl, R<sup>4</sup> is hydrogen or halogen, Q is pyrazolyl, A is lower alkylene optionally substituted with oxo or hydroxy, and n is 0, 1 or 2, provided that when R<sup>3</sup> is hydrogen, R<sup>2</sup> is aryl substituted with lower alkenyl or A is lower alkylene substituted with oxo, or its salt, processes for their preparation and pharmaceutical compositions.

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 99/05289

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/16 C07D231/14 C07D231/12 A61K31/415 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 13755 A (FUJISAWA PHARMACEUTICAL CO ; MATSUO MASAOKI (JP); OKUMURA KAZUO (JP) 17 April 1997 (1997-04-17) claim 1	2-12
A	TSUJI ET AL: "Studies on anti-inflammatory agents. V. Synthesis and pharmacological properties of 3-(difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole and related compounds" CHEMICAL AND PHARMACEUTICAL BULLETIN, JP, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, vol. 45, no. 9, September 1997 (1997-09), pages 1475-1481, XP002112607 ISSN: 0009-2363	2-12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

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- "E" earlier document but published on or after the international filing date
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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

15 March 2000

Date of mailing of the international search report

24/03/2000

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

Int. Appl. No.  
PCT/JP 99/05289

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TSUJI ET AL: "Studies on anti-inflammatory agents. IV. Synthesis and pharmacological properties of 1,5-diarylpiperazines and related derivatives"</p> <p>CHEMICAL AND PHARMACEUTICAL BULLETIN, JP, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, vol. 45, no. 6, June 1997 (1997-06), pages 987-995, XP002112608 ISSN: 0009-2363</p>	2-12
A	<p>US 5 486 534 A (LEE LEN F ET AL) 23 January 1996 (1996-01-23)</p>	2-12

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/ 05289

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 10  
is directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compounds.
2. ☒ Claims Nos.: 1  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to claim 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 99/05289

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		US 5756530 A	26-05-1998